IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Senanayake *et. al.*	Confirmation No.:	4449
Serial No.:	09/998,195	Art Unit:	1621
Filed:	December 3, 2001	Examiner:	Kumar, Shailendra
For:	SYNTHESIS, METHODS OF USING, AND COMPOSITIONS OF HYDROXYLATED CYCLOBUTYLALKYLAMINES	Attorney Docket No: CAM:	4821-409-999 208423-999408

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the provisions of 35 U.S.C. §134 and 37 C.F.R. 41.37, an appeal is taken herein from the final rejection dated March 20, 2008, which rejects claims 2-6 and 74-78 of this application. Also submitted herewith is the fee under 37 C.F.R. §41.20(b)(2), which will be paid electronically via EFS Web.

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I. REAL PARTY IN INTEREST

The real party in interest is Sepracor Inc., the assignee of record of the above-identified application.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their legal representatives respectfully submit that they are not aware of any appeals, interferences, or judicial proceedings that may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 2-6 and 74-78 of this application are under final rejection.

Claims 9-31 and 44-73 were previously canceled without prejudice in response to the Restriction Requirement dated September 8, 2003.

Claims 1, 7-8, and 32-43 were previously canceled without prejudice in an Amendment filed December 14, 2006.

New claims 79-82 are added.

Claims 2-6 and 74-82 are the subject of this appeal.

IV. STATUS OF AMENDMENTS

Claims 2-4 and 74-76 are amended to remove the term "clathrate" and "prodrug."[1]

Claims 5, 6, 77, and 78 are amended, and new claims 79-82 are added, for purposes of grouping the instant claims for presentation in this appeal. Specifically, claims 5 and 6 are amended to remove their dependency from claim 3. Claims 77 and 78 are amended to remove their dependency from claim 75. New claims 79-82 are added to recite the subject matter removed from claims 5, 6, 77, and 78 by these amendments. No new matter is added.

A listing of claims showing the claim amendments made herein, as well as a clean copy of the claims on appeal, are presented in the **CLAIMS APPENDIX** of this paper.

[1] These claims amendments are made without prejudice and solely to promote the allowance of this application.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claims on appeal recite, *inter alia*, hydroxylated sibutramine, hydroxylated alkylamino derivatives of sibutramine, and hydroxylated dialkylamino derivatives of sibutramine, as well as pharmaceutically acceptable salts, solvates, or hydrates thereof. The claims on appeal further recite, *inter alia*, pharmaceutical compositions comprising hydroxylated sibutramine, hydroxylated alkylamino derivatives of sibutramine, and hydroxylated dialkylamino derivatives of sibutramine, as well as pharmaceutically acceptable salts, solvates, or hydrates thereof.

With regard to the independent claims on appeal, claim 2 recites, *inter alia*, 1-hydroxylated sibutramine, 1-hydroxylated alkylamino derivatives of sibutramine, and 1-hydroxylated dialkylamino derivatives of sibutramine, as well as pharmaceutically acceptable salts, solvates, or hydrates thereof. (*See, e.g.*, Specification, page 5, line 28 to page 6, line 12; page 8, Scheme 4; page 10, lines 23-26; page 12, line 15 to page 13, line 19; page 15, line 10 to page 16, line 5; and page 59 line 17 to page 74, line 10).

Claim 3 recites, *inter alia*, 3-hydroxylated sibutramine, 3-hydroxylated alkylamino derivatives of sibutramine, and 3-hydroxylated dialkylamino derivatives of sibutramine, as well as pharmaceutically acceptable salts, solvates, or hydrates thereof. (*See, e.g.*, Specification, page 5, line 28 to page 6, line 8; page 6, lines 12-15; page 7, Scheme 5, page 10, lines 26-30; page 12, line 15 to page 13, line 2; page 13, line 20 to page 14, line 15; page 16, lines 1-5; and page 87, line 20 to page 95, line 19).

Claim 4 recites, *inter alia*, 7-hydroxylated sibutramine, 7-hydroxylated alkylamino derivatives of sibutramine, and 7-hydroxylated dialkylamino derivatives of sibutramine, as well as pharmaceutically acceptable salts, solvates, or hydrates thereof. (*See, e.g.*, Specification, page 5, line 28 to page 6, line 8; page 6, lines 15-17; page 7, Scheme 6; page 10, lines 20-23; page 12, line 15 to page 13, line 2; page 15, line 3 to line 9; page 16, lines 1-5; and page 74, line 11 to page 87, line 18).

Claim 74 recites, *inter alia*, pharmaceutical compositions comprising 1-hydroxylated sibutramine, 1-hydroxylated alkylamino derivatives of sibutramine, and 1-hydroxylated dialkylamino derivatives of sibutramine, as well as pharmaceutically acceptable salts, solvates, or hydrates thereof. (*See, e.g.*, Specification, page 5, line 28 to page 6, line 12; page

8, Scheme 4; page 10, lines 23-26; page 12, line 15 to page 13, line 19; page 15, line 10 to page 16, line 16; and page 59 line 17 to page 74, line 10).

Claim 75 recites, *inter alia*, pharmaceutical compositions comprising 3-hydroxylated sibutramine, 3-hydroxylated alkylamino derivatives of sibutramine, and 3-hydroxylated dialkylamino derivatives of sibutramine, as well as pharmaceutically acceptable salts, solvates, or hydrates thereof. (*See, e.g.*, Specification, page 5, line 28 to page 6, line 8; page 6, lines 12-15; page 7, Scheme 5, page 10, lines 26-30; page 12, line 15 to page 13, line 2; page 13, line 20 to page 14, line 15; page 16, lines 1-16; and page 87, line 20 to page 95, line 19).

Claim 76 recites, *inter alia*, pharmaceutical compositions comprising 7-hydroxylated sibutramine, 7-hydroxylated alkylamino derivatives of sibutramine, and 7-hydroxylated dialkylamino derivatives of sibutramine, as well as pharmaceutically acceptable salts, solvates, or hydrates thereof. (*See, e.g.*, Specification, page 5, line 28 to page 6, line 8; page 6, lines 15-17; page 7, Scheme 6; page 10, lines 20-23; page 12, line 15 to page 13, line 2; page 15, line 3 to line 9; page 16, lines 1-16; and page 74, line 11 to page 87, line 18).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issue presented on appeal is whether the Examiner erred in rejecting claims 2-6 and 74-78 (*i.e.*, instant claims 2-6 and 74-82)[2] as allegedly obvious under 35 U.S.C. §103 over Jeffery *et. al, J. Chem. Soc. Perkin Trans.*, 1: 2583-9 (1996) ("Jeffery") and Housley *et al.*, U.S. Patent No. 5,047,432 ("Housley").

Specifically, the issues below are presented on appeal to this Board:

1. Whether the Examiner erred in rejecting the subject matter recited in instant claims 2, 4-6, 74, and 76-78[3] as allegedly obvious over Jeffery and Housley; and

[2] Claims 2-6 and 74-78 were rejected in the Final Office Action dated March 20, 2008. The subject matter of these claims are recited in instant claims 2-6 and 74-82, following the entry of the amendments and new claims presented herein.

[3] Instant claims 2, 4-6, 74, and 76-78 recite, *inter alia*, 1-hydroxylated and 7-hydroxylated sibutramine and sibutramine derivatives, as well as pharmaceutical compositions comprising the same.

II. Whether the Examiner erred in rejecting the subject matter recited in instant claims 3, 75, and 79-82[4] as allegedly obvious over Jeffery and Housley.

VII. ARGUMENT

A. Background of the Invention.

Sibutramine, chemically named [N-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-N,N,-dimethylamine, is a neuronal monoamine reuptake inhibitor. Sibutramine inhibits the reuptake of norepinephrine, serotonin and dopamine. Racemic sibutramine is sold as a hydrochloride monohydrate under the tradename MERIDIA® and is indicated for the treatment of obesity. Further, Sibutramine can be used in the treatment of a variety of other disorders, including depression, Parkinson's disease, and senile dementia.

In humans, sibutramine is rapidly absorbed from the gastrointestinal tract following oral administration and undergoes an extensive first-pass metabolism. This metabolism yields the primary metabolites desmethylsibutramine and didesmethylsibutramine, as shown in Figure 1 below.

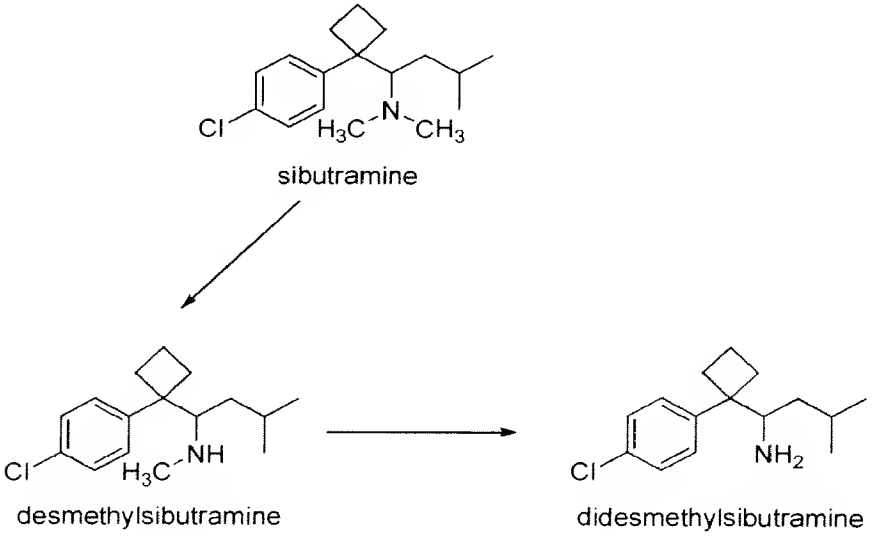
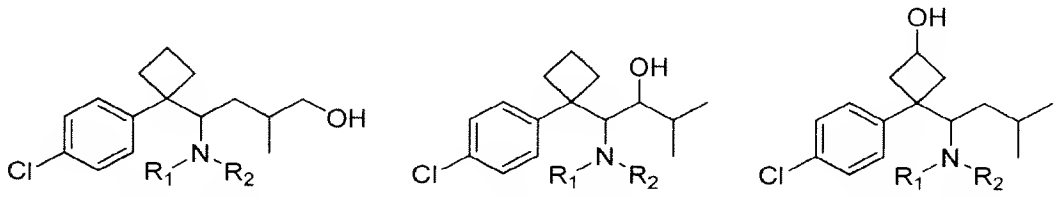


Figure 1. Metabolism of sibutramine.

[4] Instant claims 3, 75, and 79-82 recite, *inter alia*, 3-hydroxylated sibutramine and sibutramine derivatives, as well as pharmaceutical compositions comprising the same.

The instant application relates to 1-hydroxylated, 3-hydroxylated, and 7-hydroxylated sibutramine and its derivatives, as well as pharmaceutically acceptable salts, solvates, or hydrates thereof.



1-hydroxylated derivative | 3-hydroxylated derivative | 7-hydroxylated derivative

Figure 2. Hydroxylated derivatives of sibutramine.

B. Summary of Prosecution History.

The instant application was filed on December 3, 2001. The instant application claims priority from U.S. Provisional Application No. 60/257,052, filed December 22, 2000 and U.S. Provisional Application No. 60/250,524, filed December 4, 2000. As can be seen from this filing date, this application has a lengthy prosecution history.

On September 8, 2003, the USPTO issued a Restriction Requirement. On September 7, 2003, Appellants responded to this Restriction Requirement and provisionally elected, with traverse, "Group I" (claims 1-8 and 32-43). Further, in response to the Office's requirement under 35 U.S.C. §121 to elect a single disclosed species, Appellants elected 4[1-(4-chloro-phenyl)-cyclobutyl]-2-methyl-4-methylamino-butan-1-ol.

On December 10, 2003, a non-final Office Action was mailed. Claims 1-2, 4-8, 32-39, and 42-43 were rejected under 35 U.S.C. §102 as allegedly anticipated by Jeffery *et al*, *J.Chem. Soc., Perk Trans*, 1, 1996, pp 2583-2589, ("Jeffery"). (Office Action dated December 10, 2003, page 2). Specifically, the Examiner alleged that these claims were anticipated by compounds 4 and 5a of Jeffery. (*Id.* at page 3). Further, the Examiner rejected claims 1-8 and 32-43 under 35 U.S.C. §103 as allegedly unpatentable over Jeffery. (*Id.* at pages 3-4). Specifically, the Examiner alleged:

> Jeffery *et al.* teach structurally similar compounds and composition as claimed herein, see page 2583, compound 4 and 5a. The difference between the reference and herein claimed compound appears to be OH position in the

> compound. In herein, OH can be at position 3 also, whereas no such positional isomer has been taught in the reference. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain compounds within the generic structure of the reference, because the reference is structurally so similar to those claimed herein, except the OH position is different, with the reasonable expectation of achieving a successful composition, absent evidence to the contrary. Note that positional isomers are prima facie obvious.

(*Id.*, (citing *In re Norris*, 179 F.2d 970 (C.C.P.A. 1950))).

In a Response filed April 12, 2004, Appellants pointed out that claims 1-2, 4-8, 32-39, and 42-43 are not anticipated by Jeffery because compounds 4 and 5a are structures of racemic compounds. (Appellants' Response dated April 12, 2004, page 6). As explained by Appellants, the structures of compounds 4 and 5a depict cis/trans isomerization and do not depict stereomerically pure forms. (*Id.* at page 6, FN 1). Further, Appellants pointed out that claims 1-8 and 32-43 are not obvious in part because Jeffery teaches away from the claimed compounds. (*Id.* at page 7). Specifically, Appellants pointed out that "Jeffery reports that the pharmacological activity of sibutramine is 'mediated predominantly by' two demethylated amines of sibutramine (compounds 2 and 3), implying that compounds 4 and 5a contribute little to sibutramine's pharmacological activity." (*Id.*, (Jeffery page 2583)).

On June 17, 2004, a final Office Action was mailed. The rejection under 35 U.S.C. 102 was withdrawn. (Office Action dated June 17, 2004, page 2). However, the Examiner maintained the rejection under 35 U.S.C. §103 and alleged that

> The expectation with regard to enantiomers is that activities as they pertain to living systems are expected to be different...The fundamentals of optical activity and stereoisomerism are well known to person having ordinary skill in the art. A person having ordinary skill in the art would have known how to resolve the racemic mixture and would have been motivated to do so with the reasonable expectation of achieving enantiomers having substantially different pharmacological activity. It appears as though applicants have determined experimentally what a person of ordinary skill in the art would have expected, namely that the racemic mixture of the prior art may be separate (+) and (-) enantiomers possessing substantially different pharmacological activity. This is an expected result.

(*Id.* at pages 2-3, *citing In re Adamson*, 275 F.2d 952 (C.C.P.A. 1960)).

In a Response filed August 17, 2004, Appellants reiterated that Jeffery teaches away from the claimed compounds because "Jeffery discloses that the pharmacological activity of

sibutramine is mediated predominantly by sibutramine metabolites other than those claimed in this application." (Appellants' Response dated August 17, 2004, page 3). Appellants noted that the Examiner improperly ignored this teaching away. (*Id.*). Further, Appellants pointed out that the Examiner's reliance on *In re Adamson* was misplaced. (*Id.*). Specifically, Appellants explained that:

> *In re Adamson* concerned claims directed to an L-isomer of a chemical compound having substantially higher spasmolytic activity than the D-isomer of the same compound...The spasmolytic activity and structure of the compound were disclosed in the prior art...To the contrary, the pharmacological activity of the claimed compounds is not disclosed in Jeffery. In fact, Jeffery teaches that the claimed compounds are likely to be pharmacologically inactive. Therefore, Applicants respectfully submit that the principles of In re Adamson are not applicable in this application.

(*Id.* (internal citations omitted)).

On August 30, 2004, an Advisory Action was mailed. The Examiner maintained the rejection under 35 U.S.C. §103 "for the reasons of record" and because "[n]o unexpected results have been shown." (Advisory Action dated August 30, 2004).

On January 18, 2005, Appellants filed a Response, along with a Request for Continued Examination. Appellants noted that the Examiner once again did not offer a response to Appellants' arguments that Jeffery teaches away. (Appellants' Response dated January 18, 2005, page 3). Appellants further noted that, as well settled, "each obviousness determination should rest on its own facts." (*Id.* at page 3). Specifically, Appellants explained that "*prima facie* obviousness of a claimed compound cannot be established if its assertion is based on nothing more than a structural similarity between the claimed compound and those in the prior art." (*Id.* at page 3, (citing *Yamanouchi Pharm. Co., Ltd. V. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000))).

On February 9, 2005, a non-final Office Action was mailed. The Examiner rejected claims 1-8 under 35 U.S.C. §103(a) as being allegedly unpatentable over the combined teachings of Jeffery, U.S. Patent No. 6,331,571 ("Jerussi") and Fang *et al.*, *Tetrahedron: Asymmetry*, 10 4477-4480 (1999) ("Fang"). (Office Action dated February 9, 2005, page 2). Specifically, the Examiner alleged:

> Jeffery et al. teach structurally similar compounds as claimed herein. See page 2583, compound 4 an 5a. Compound 5 expressly suggest

> stereoisomerisms similar to claimed herein. The difference between the reference and herein claimed compounds is the hydroxyl substituent at different positions. Jerussi et al is teaching structurally similar compounds as claimed herein, which have different stereoisomerisms, as claimed herein...Likewise, Fang et al. is teaching preparation of enantiomerically pure sibutramine and its metabolite, which is similar in the instant specification. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain compounds of Jeffery et al having hydroxyl substituents in different positions, and obtain enantiomers using the process of Jerussi et al. and Fang et al., with the reasonable expectation of achieving a successful enantiomers and their pharmaceutical compositions, absent evidence to the contrary. Note that positional isomers are prima facie obvious.

(*Id.* at pages 2-3 (citing *In re Norris*, 179 F.2d 970 (C.C.P.A. 1950))).

Further, in response to Appellants' point that Jeffery does not teach stereomerically pure compounds, the Examiner alleged that "Applicants' arguments that stereoisomerisms have not been taught by Jeffery is not convincing. See compound 5a. Also see Jerussi et al. and Fang et al., which expressly teach the enantiomers and the process of preparing enantiomers." (*Id.* at page 3).

In addition, with regard to Appellant's point that Jeffery teaches away, the Examiner alleged that:

> Applicants' arguments that Jeffery disclose that the pharmacological activity of sibutramine is mediated predominantly be sibutramine metabolites other than those claimed in this application is of little if any probative value inasmuch as the reference teach structurally similar compounds and its enantiomers. Applicants argue that...Jeffery [teaches] that their compounds are pharmacologically inactive. The examiner did not find such a statement in the reference. Notwithstanding that, Jerussi et al. and Fang et al. expressly teach that sibutramine are pharmacologically active.

(*Id.* at pages 3-4).

In a Response filed May 5, 2005, Appellants first pointed out that Jerussi is not prior art under 35 U.S.C. 103(c) because the instant application and Jerussi were commonly owned by Sepracor Inc. at the time of the filing of the instant application. (Appellants Response dated May 5, 2005, page 2). Next, Appellants explained that while compound 5a shows cis/trans isomerism, the compound is not stereomerically pure. (*Id.* at 3).

With respect to the Examiner's allegations regarding Fang, Appellants pointed out that:

> Fang adds nothing to the substance of the rejection. This is because Fang merely discloses the enantiomers of sibutramine and desmethylsibutramine, none of which are encompassed by the pending claims. Furthermore, while Fang discloses the preparation of enantiomers, it is silent as to their desirability. Therefore, Fang would not have provided those of ordinary skill in the art with any motivation [to] modify Jeffery so as to obtain the stereoisomers recited by the pending claims.

(Appellants' Response dated May 5, 2005, page 3).

In response to the Examiner's allegation that positional isomers are *prima facie* obvious, Appellants pointed out that "the claimed compounds are not mere positional isomers of the compounds disclosed in Jeffery, but are instead stereoisomers of positional isomers...stereoisomers, much less stercoisomers of positional isomers, are not *per se* obvious over the racemic compounds." (*Id.* at page 3).

In response to the Examiner's allegation that the fact that Jeffery teaches away "is of little if any probative value inasmuch as the reference teach structurally similar compounds and its enantiomers," Appellants once again explained that Jeffery does not teach stereomerically pure compounds. Further, Appellants noted that allegations based on structural similarity cannot form the basis of an obviousness determination. Specifically, as Appellants explained,

> The pending claims are not obvious because Jeffery provides no reason or motivation to make the claimed compounds. Indeed, Jeffery clearly implies that the claimed compounds contribute little to sibutramine's activity, thereby discouraging those of ordinary skill in the art from making and using the claimed compounds. Without providing any evidence or argument that refutes the well-established legal principle or Applicants' arguments, the Examiner merely concludes that such arguments have little value because Jeffery teaches compounds that are structurally similar to the claimed compounds. Such a conclusory statement simply begs the question, and cannot form the basis for an obviousness rejection.

(*Id.* at pages 3-4, internal citations omitted).

On July 25, 2005, a final Office Action was mailed. The Examiner withdrew Jerussi as a reference. However, the Examiner maintained the rejection under 35 U.S.C. §103(a). The Examiner alleged the following:

> Applicants argue that Jeffery does not suggest stereoisomers. The examiner disagrees...The examiner does not understand applicants' arguments that Fang disclose the preparation of enantiomers but is silent as to their desirability, and none of the compounds are claimed herein. At the outset, inasmuch as the preparation is there, the desirability is there too. With reference to hydroxy substituent, note a combination of the references have been used. Examiner also does not understand applicants' statement that instant claims are stereoisomers of the positional isomers. Given that, Jeffery et al. are teaching structurally similar compounds as claimed herein, and Fang et al are teaching preparation of enantiomerically pure sibutramine and its metabolite, there is indeed motivation to arrive at the claimed enantiomers, absent evidence to the contrary.

(Office Action dated July 25, 2005, pages 2-3).

On September 28, 2005, Appellants filed a response. With regard to Jeffery, Appellants pointed out that Jeffery fails to teach the claimed compounds. (Appellants' Response dated September 28, 2005, page 2). Appellants reiterated that compounds 4 and 5a of Jeffery are not stereomerically pure. (*Id.*). Further, Appellants, once again, pointed out that Jeffery actively teaches away from the claimed invention by providing that the pharmacological activity of sibutramine is "mediated predominantly by" two demethylated amines of sibutramine, which are not encompassed by the claims. (*Id.* at page 3).

Appellants further pointed out that Fang does not cure the defects of Jeffery. Specifically, Appellants noted that "Fang merely discloses the enantiomers of sibutramine and desmethylsibutramine, none of which are encompassed by the pending claims." (*Id.*). As Appellants explained, "although Fang discloses the synthesis of enantiomers of sibutramine and its metabolite, which are not encompassed by the pending claims, it discloses nothing with regard to the desirability of enantiomers in general, much less the claimed enantiomers. (*Id.*).

In response to the Examiner's allegation that "inasmuch as the preparation is there, the desirability is there too," Appellants stated:

> this statement is based on the Examiner's misunderstanding of what Fang discloses. As Applicants pointed out, Fang does <u>not</u> disclose the preparation of the <u>claimed compounds</u>. Rather, Fang discloses the preparation of compounds that are not encompassed by the pending claims. Further, Fang does not provide anything regarding whether the claimed compounds are useful. Combining this fact with Jeffery's disclosure that pharmacological activity of sibutramine predominantly comes from its metabolites that are not

> encompassed by the pending claims, it is clear that little motivation to combine or modify these two references would have existed.

(*Id.* at page 4 (emphasis added)).

Finally, Appellants pointed out that contrary to the Examiner's allegation, positional isomers are not *prima facie* obvious. (*Id.*). Instead, each obviousness determination should rest on its own facts. (*Id.*).

On October 17, 2005, an Advisory Action was mailed. The Examiner alleged that Appellants' remarks of September 28, 2005 did not place the application in condition for allowance because "stereoisomers are obvious over racemates and methods to prepare stereoisomers are old in the art and well known." (Advisory Action dated October 17, 2005).

On November 14, 2005, Appellants filed a response. Appellants pointed out that the Examiner's allegation that "stereoisomers are obvious over racemates" is flatly contrary to the well-established principles governing the non-obviousness of compounds. (Appellants Response dated September 14, 2005, page 3). Appellants pointed out that "such a conclusory statement cannot form a basis for a prima facie case of obviousness." (*Id.* at page 4). Appellants noted that "[g]eneralization should be avoided insofar as specific chemical structures are alleged to by prima facie obvious one from another." (*Id.* at page 3 (quoting *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985))). Thus, as Appellants explained, "*prima facie* obviousness of a claimed compound cannot be established if its assertion is based on nothing more than a structural similarity between the claimed compound and those in the prior art." (*Id.*).

On December 1, 2005, a final Office Action was mailed. The Examiner maintained the rejection under 35 U.S.C. §103(a) and stated:

> [t]he examiner would like to point out that again, that stereoisomer is prima facie obvious over racemate, as a whole, absent evidence to the contrary. The examiner has not seen any where, in the instant specification, any unexpected results and applicants have not argued in terms of any unexpected results, and claims are unpatentable.

(Office Action dated December 1, 2005 (internal citations omitted)).

Appellants filed a Response on May 18, 2006. Appellants pointed out again that Jeffery teaches away from the instant application. (Appellants' Response dated May 18,

2006, page 2). Appellants submitted a copy of this Board's decision in *In re Holy*, 2004 WL 77012 (B.P.A.I. 2004), which addressed issues almost identical to the instant case (*Id.*):

> [i]n *Holy*, claims at issue recited a genus of enantiomerically pure chemical compounds. The claims were rejected under 35 U.S.C. §103 over, among others, a reference which disclosed a racemic mixture of a compound encompassed by the chemical structure recited by the claims. The examiner in *Holy*, rejected the claims as allegedly obvious, citing *In re Adamson* and providing a reasoning substantially identical to that provided in the present application by the Examiner, *i.e.*, that a stereoisomer is *prima facie* obvious over prior disclosure of its racemic mixture.

(*Id.* at pages 2-3 (citing *In re Holy*) (internal citations omitted)). Appellant noted that this Board reversed the examiner's rejection and stated:

> [i]n order to make a *prima facie* case of obviousness based on the structural similarity, in this case similarity between the claimed optical isomer and its racemate taught by the prior art, not only must the structural similarity exist, but the prior art must also provide reason or motivation to make the claimed compound.

(*Id.* at page 3 (citing *In re Holy*)).

> Next, Appellants explained:

> [t]he Board went on to hold that the rejection cannot be sustained because the references cited by the examiner in *Holy* did not provide any motivation, and the examiner did not 'set forth any facts or findings to support the motivational statement, especially since all that is currently being claimed is a single stereoisomer.'

(*Id.* (citing In re Holy)). Further, Appellants pointed out that this Board rejected the examiner's reliance on *Adamson* for the proposition that stereoisomers are *per se* obvious over a racemic mixture because "one cannot rely on case law alone...to provide the motivation to modify a prior art compound." (*Id.* (citing *In re Holy*)).

> Appellants pointed out that:

> the facts and holdings of Holy are directly applicable to the present application. As in Holy, the Examiner's rejection is based solely on the allegation that a stereoisomer is prima facie obvious over the prior disclosure of its racemate. As in Holy, the Examiner relies on cases to provide support for his allegation, without any consideration as to whether prior art as a whole would have provided any motivation...Therefore, Applicants respectfully submit that the rejection of the claims...cannot be sustained.

(*Id.* at pages 3-4).

On May 31, 2006, an Advisory Action was mailed. The Examiner alleged that the Appellants Response of May 19, 2006 failed to place the application in order for allowance for reasons of record.

In a Response filed December 14, 2006, Appellants reiterated that 1) Jeffery fails to teach the claimed compounds; 2) compounds 4 and 5a of Jeffery are not stereomerically pure; 3) Jeffery teaches away from the instant compounds; 4) Fang does not teach or suggest the instant compounds; and 5) this Board's decision in *In re Holy* evidences the non-obviousness of the instant compounds. (Appellants Response dated December 13, 2006, pages 5-9).

On January 19, 2007, a non-final Office Action was mailed. Claims 2-6 and 74-78 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Jeffery. To Appellants' surprise, the Examiner, once again, alleged that Jeffery teaches stereoisomers, an issue that Appellants thought was clarified with the Examiner. (Office Action dated January 19, 2007, page 2). Specifically, the Examiner alleged that compounds 4, 5a, and 5b of Jeffery are stereoisomers. (*Id.* at pages 2-3). The Examiner further alleged:

> [t]he difference between the reference and herein claimed compounds and composition is that the reference has not made every derivative that is claimed. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify Jeffery...and obtain other derivatives, as the other derivatives are no more than positional isomers, with the reasonable expectation of achieving a successful composition, absent evidence to the contrary. Note that positional isomers are prima facie obvious.

(*Id.* at page 3). The Examiner further alleged:

> Applicants arguments were fully considered and were not found convincing. Applicants allege that Jeffery fails to teach claimed compounds. The examiner disagrees. Compound 5a and other compounds cited...are same compounds as claimed herein. Applicants further argue that the reference does not teach stereomerically pure compound[s]. The examiner disagrees. See compound 5a, [compound 5b and compound 4]...Inasmuch as the reference is teaching stereoisomeric compound, claims are rendered prima facie obvious. Applicants further allege that there is no motivation to make the stereoisomers from the Jeffery reference. Not page 2587, column 2, the reference has made stereoisomeric compounds.

(*Id.*).

Yet another Response was filed on June 18, 2007. First, Appellants pointed out, once again, that Jeffery does not disclose stereomerically pure compounds. (Appellants' Response dated June 18, 2007 page 5). Specifically, Appellants explained to the Examiner that compounds 5a and 5b merely depict cis/trans isomerism. (*Id.*). Further, Appellants noted that compound 4 was isolated in Jeffery as a mixture of diastereomers – no attempts were made in Jeffery to separate out the diastereomers. (*Id.* at pages 5-6). Appellants also noted that Jeffery does not suggest the desirability of any stereoisomer. (*Id.*). Next, Appellants pointed out, once again, that Jeffery teaches away from the instant invention.

On July 2, 2007, a personal interview was held. Appellants discussed this Board's decisions in *In re Holy* and *In re Barberich*[5], Appeal No. 2005-0906. Appellants pointed out that Jeffery does not teach stereomerically pure compounds. The Examiner, in the Interview Summary, noted that he "would study these case laws and reconsider his position."

However, on September 12, 2007, a non-final Office Action was mailed. Claims 2-6 and 74-78 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the combined teachings of Jeffery and Housley, U.S. Patent No. 5,047, 432 ("Housley"). (Office Action dated September 12, 2007, page 2). The Examiner alleged, once again, that Jeffery "teaches stereoisomers of hydroxylated derivative[s] of sibutramine." (*Id.*). Specifically, the Examiner pointed to compounds 4, 5a, and 5b of Jeffery. (*Id.*). With regard to Housley, the Examiner alleged:

> [Housely] is teaching structurally similar compounds as claimed inherein can exist in different optically active form, when the compounds contain one chiral center, the compounds can exist in two enantiomeric forms. When the compounds contain more than one chiral center, the compounds can exist in diastereoisomeric forms, similar to claimed herein. Even geometric isomeric compounds have been taught.

(*Id.*). Further, the Examiner pointed to column 5, lines 48-60 and the compound on column 7, lines 48-49. (*Id.*). Next, the Examiner alleged that

> [i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify Jeffery...by including diastereoisomers and multiple chiral centers in the compounds as thought by Housley...because the latter reference is expressly teaching that diastereoisomers and multiple chiral centers are old in the structurally similar compounds.

[5] Discussed fully in section C, *infra*.

(*Id.* at pages 2-3). Further, the Examiner alleged that "Appilcants' arguments were fully considered and were not found convincing, especially in view of [Housley]. Applicants point out to [compound 5a] and suggest[] that they disclose cis/trans isomer[s]. However, Housley...is expressly teaching that these compounds can exist in various stereoisomeric forms." (*Id.* at page 3).

Lastly, the Examiner rejected the precedent set forth by this Board in *In re Holy* and *In re Barberich.*

On December 6, 2007, Appellants filed a Response. Appellants directed the Examiner's attention to *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350 (Fed. Cir. 2007). (Appellants' Response dated December 6, 2007, pages 6-7). Specifically, Appellants pointed out that as the Federal Circuit stated, "in cases involving new chemical compounds, in remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." (*Id.* (quoting *Takeda*)). Appellants further cited numerous cases showing that allegations of structural similarity is not a proper basis for a *prima facie* obviousness. Next, Appellants, once again, explained to the Examiner that compounds 4, 5a, and 5b of Jeffery are not stereomerically pure. (*Id.* at pages 7-8). Specifically, Appellants pointed out that the stereocenters of the cited compounds were not defined in Jeffery. (*Id.*). With regard to Housley, Appellants pointed out that, contrary to what is claimed in the instant application, the cited compound is not stereomerically pure. (*Id.* at page 9). Further, Appellants noted that Formula 1 of Housley discloses a genus that encompasses millions of compounds, but would not have provided any motivation to specifically single out any particular compound. (*Id.* at page 9). Appellants further noted that while Housley discloses species of compounds, hundreds of species are disclosed with no indication as to the desirability of singling out any particular species. (*Id.* at page 9).

In addition, Appellants reiterated the principles set forth by this Board in *In re Holy*. (*Id.* at page 10). Appellants also reiterated that Jeffery teaches away from the instant claims. (*Id.*).

On March 20, 2008, a final Office Action was mailed. The Examiner maintained the rejection of claims 2-6 and 74-78. (Office Action dated March 20, 2008, page 3). In the Examiner's own words:

> Applicants arguments were fully considered and are not found convincing. Applicants allege that the examiner's positions of similarity of the instant claimed compounds and the reference compounds is improper, and cites In re *Langer et al.* While, *In re Langer* differs in terms of 3 carbon atoms and are directed to 5 to 7 membered rings, the instant claims are directed to structurally similar compounds as claimed herein: see [compound 5a]. Applicants further alleged that none of the compounds pointed to by the examiner to Jeffery...are stereomerically pure, and Jeffery merely points out to cis/trans isomerism. And with respect to stereoconfirugation (R and S), the reference is silent. The examiner would like to point out that inasmuch as applicants have shown the structure of Jeffery...in terms of the stereocenters, even though, the reference does not mention those centers, the carbon having four difference atoms on it, automatically is entitled to the stereocenters and especially in view of Housley, one of ordinary skill in the art would be motivated to isolate the same. Applicants' allegations that millions of compounds can be generated from Housley's reference appears to be exaggerated, especially when the examiner has particularly pointed out to the specific compound in column 7. There is certainly no lack of motivation in herein, especially when chiral centers exist and there are well known methods of deriving the isomers. Applicants' arguments with respect to *In re Holy* is not valid in herein, because in the Jeffery...the teaching is not specific to the racemic compounds. There is enough suggestion to arrive at the stereocenters, specifically in view of the chiral carbon atom. Applicants' arguments with respect to Jeffery...that the reference teaches away from the instant claimed compounds are not convincing, especially when taken together with the Housley...reference.

(*Id.* at page 3-4).

This appeal followed.

C. The Examiner erred in rejecting the subject matter recited in instant claims 2, 4-6, 74, and 76-78 as allegedly obvious over Jeffery and Housley.

The Examiner erred in rejecting the subject matter recited in instant claims 2, 4-6, 74, and 76-78 as allegedly obvious over Jeffery and Housley because:

1. The Examiner did not establish a *prima facie* case of obviousness; and

2. Even assuming, *arguendo*, a *prima facie* case were established, Jeffery rebuts such a *prima facie* case because it teaches away from the instantly claimed compounds.

1. The Examiner has not established a *prima facie* case of obviousness.

a. A *prima facie* case of obviousness requires a showing that a person of ordinary skill in the art would have had reason to attempt to make the claimed invention and would have had a reasonable expectation of success in doing so.

The standard for obviousness under 35 U.S.C. §103 was recently clarified in the landmark decision of *KSR International Co. v. Teleflex Inc.* (127 S.Ct. 1727, 167 L.Ed.2d 705, 75 USLW 4289, 82 U.S.P.Q.2d 1385 (2007)). In *KSR*, the Supreme Court held that the application of the "teaching, suggestion, motivation" test is not mandatory in determinations of obviousness under 35 U.S.C. §103 and cautioned against the use of "rigid and mandatory formulas." (*Id.* at 1741). However, the Court nonetheless emphasized that determinations of obviousness based on hindsight analysis is still improper. Indeed, the Court warned that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." (*Id.*). As the Court explained, this is because "inventions in most, if not all instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*Id.*). As such, the Court stated that the TSM test "captured a helpful insight" because it is important "to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." (*Id.*).

In light of this holding, in decisions following *KSR*, the Federal Circuit and District Courts have required a showing that one skilled in the art would have had a reason to combine or modify prior art elements in assessing (non)obviousness under 35 U.S.C. §103. (*See, e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007) (patent challenger alleging obviousness must show "by clear and convincing evidence that a person of ordinary skill in the art would have had reason to make the composition of device, or carry out the claimed process..."); *Takeda Chemical Industries, Ltd. v. Alphapharm Pty.*, Ltd. 492 F.3d 1350 (C.A.Fed. (N.Y.)), 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007) ("it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound"); *Bayer AG v. Dr. Reddy's Labs, Inc.*, 2007 WL 3120794 (D. Del. 2007) (Chemical composition claims held to be unobvious in part because defendant did not show "by clear and

convincing evidence, that a person of ordinary skill in the art would have had a reason to attempt to make the claimed compositions...")).

Further, as the Supreme Court in *KSR* explained, an obviousness determination takes into account whether the combination of elements would yield "anticipated success" or "predictable results." (*Id.* at 1739). As such, following the *KSR* decision, the Federal Circuit has based determinations of obviousness on whether a claimed combination would have yielded "predictable results" or whether there would have been "a reasonable expectation of success" in the claimed invention. (*See, e.g., In re Trans Tex. Holdings Corp*, 498 F.3d 1290 (Fed. Cir. 2007) (determination of obviousness for a patent relating to stem cell research based on whether the combination yielded "predictable results"); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007) (patent challenger must show by "clear and convincing evidence" that there would have been a "reasonable expectation of success"); *Aventis Pharma Deutschland GmbH v. King Pharms, Inc.* 499 F.3d 1293, 1301 (Fed. Cir. 2007) (determination of obviousness based on whether the prior art provided an "expectation" that claimed compounds would have the intended properties)). The District Courts have also taken this approach. (*See, e.g., Friskit Inc. v. Real Networks, Inc.*, 499 F.Supp2d 1145 (N.D. Cal. 2007) (analysis under 35 U.S.C. §103 for patent related to streaming content based on whether prior art elements were "integrated...to produce a result which was predictable"); *Boston Scientific Corp. v. Johnson & Johnson*, 2007 WL 2408870 (N.D. Cal. 2007) (defendant's summary-judgment motion of obviousness denied in part because "[i]t is unclear whether [the prior art] presented such a viable solution so as to yield predictable results") (internal quotations omitted)).

The Federal Circuit, following *KSR*, articulated guidelines for determining "whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious." (*PharmaStem*, 491 F.3d at 1364). As the Federal Circuit explained:

> [A]n invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

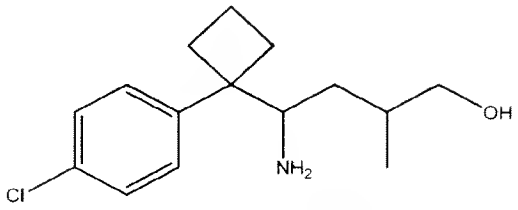
(*Id.*, (citing *In re O'Farrell*, 953 F.2d 894, 903 (Fed.Cir. 1988))(internal quotations omitted)).

In sum, on the basis of *KSR* and the Federal Circuit and District Court cases following *KSR*, the current standard of obviousness takes into account: (1) whether there would have been a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;" and (2) whether the combination of elements would have yielded "predictable results" *i.e.*, whether there would have been a reasonable expectation of success. (*See, e.g., PharmaStem* 491 F.3d at 1360 ("The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.") (emphasis added) (internal quotations omitted)).

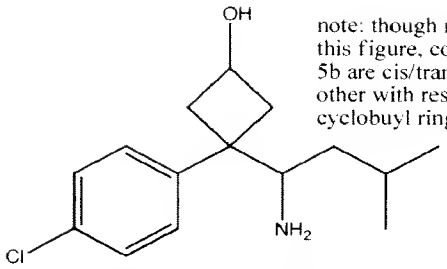
b. The Examiner has not established a *prima facie* case of obviousness.

The Examiner alleges that the subject matter recited in instant claims 2, 4-6, 74, and 76-78 are *prima facie* obvious over Jeffery and Housley. (Office Action dated March 20, 2008, page 3). However, as set forth below, the Examiner has not established a *prima facie* case of obviousness because: (1) the Examiner has not identified a reason that would have prompted a person skilled in the art to make or use the instant compounds; and (2) the Examiner has not provided anything as to why one skilled in the art would have had a reasonable expectation that the claimed compounds would possess advantageous properties.

First, Jeffery does not disclose any compounds encompassed by claim 2 or 4. While the Examiner has pointed to compounds 4, 5a and 5b of Jeffery, claims 2 and 4 recite stereomerically pure forms of these compounds, which are not disclosed by Jeffery. (*See* Figure 3, *infra*).

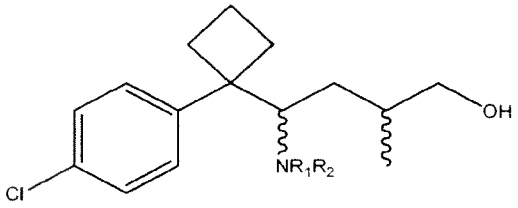


Jeffery compound 4



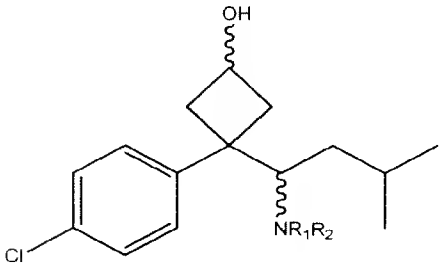
note: though not depcited in this figure, compounds 5a and 5b are cis/trans isomers of each other with respect to the cyclobuyl ring

Jeffery compounds 5a/5b



claims 2 and 74

when R_1 and R_2 are both H, the compound is stereomerically pure



claims 4 and 76

when R_1 and R_2 are both H, the compound is stereomerically pure

Figure 3

For example, with regard to compound 4 of Jeffery, the stereoconfigurations of the compound's chiral centers are not specified. (*See* Figure 4, *infra*). Indeed, as stated in Jeffery, the compound is isolated "in the form of a 3.8:1 mixture of diastereomers." (Jeffery, page 2587 (emphasis added)). No attempts were made in Jeffery to separate or isolate the diastereomers. With regard to compounds 5a and 5b, which are cis/trans isomers, Jeffery is completely silent with regard to the stereoconfiguration of the carbon bearing the isobutyl moiety. (*See* Figure 4, *infra*). Thus, Jeffery does not disclose any compounds that are encompassed by claims 2, 4-6, 74, and 76-78.

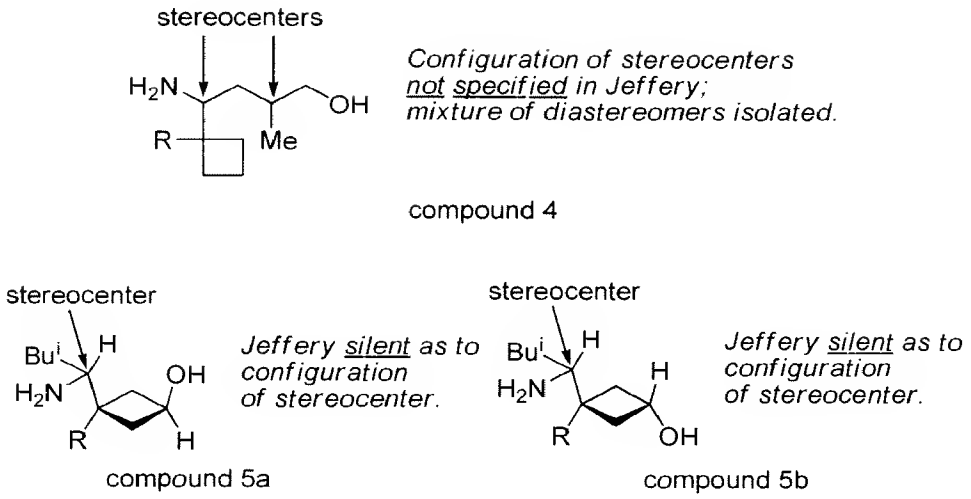


Figure 4. Compounds 4, 5a, and 5b as depicted in Jeffery.

Appellants take this opportunity to respectfully note that the Examiner appears to have misunderstood the concept of stereoisomerism over a significant portion of the prosecution history. As the prosecution history shows, the Examiner incorrectly alleged that Jeffery discloses stereomerically pure forms of compounds 4, 5a, and 5b in Office Actions dated February 9, 2005; July 25, 2005; January 19, 2007; September 19, 2007; and July 2, 2007 and improperly used such allegations as a basis for rejecting Appellants' claims, despite Appellants' repeated explanations to the contrary. (*See, e.g.*, responses filed May 5, 2005; September 28, 2005; November 14, 2005; December 14, 2006; June 18, 2007; and December 6, 2007; and personal interview held July 2, 2007). After over 3 years, the Examiner acknowledged that Jeffery does not disclose stereomerically pure forms of compounds 4, 5a, and 5b, as evidenced in the Office Action dated Mach 20, 2008.[6]

Moreover, the Examiner has not provided any reason that would have prompted one of ordinary skill in the art to specifically isolate any of the compounds encompassed by the claims 2 or 4, nor has the Examiner adequately explained why one skilled in the art would

[6] Appellants also note that at one point during the prosecution, Appellants thought that the Examiner understood that Jeffery does not disclose the claimed stereomerically pure compounds. This is evidenced by the fact that the Advisory Action dated October 17, 2005 indicates that "stereoisomers are obvious over racemates." (*See* Advisory Action dated October 17, 2005). Despite the legal flaw in this statement, it nevertheless evidences the fact that the Examiner did agree that Jeffery does not disclose the claimed stereomerically pure compounds. However, for a reason not apparent to Appellants, the allegation again appeared in the Office Action dated January 19, 2007.

have had a reasonable expectation that these compounds would possess advantageous properties. For example, the Examiner has not pointed to any reason that would have prompted one skilled in the art to isolate stereomerically pure isomers of compounds 4, 5a and 5b. Notably, nothing in Jeffery even hints the desirability of isolating such isomers.[7] Nor has the Examiner provided any reason that would have prompted those skilled in the art to isolate any of the other compounds encompassed by claim 2 or 4. For example, the Examiner has not pointed to any portion in Jeffery that would have provided insight as to the desirability of adding a 1-hydroxyl or 7-hydroxyl group to an alkylamino or a dialkylamino derivative of sibutramine. Further, the Examiner has not explained how Jeffery would have provided one skilled in the art an expectation that adding a 1-hydroxyl or a 7-hydroxyl group would result in any advantageous properties.

Housley does not cure the defects of Jeffery. Housley does not disclose any compounds that are encompassed by claim 2 or 4. Further, completely absent in Housley is any portion that would have provided a reason to one skilled in the art to isolate compounds 4, 5a, or 5b, much less in their stereomerically pure form, or any insight as to the desirability of adding a 1-hydroxyl or 7-hydroxyl group to an alkylamino or a dialkylamino derivative of sibutramine. Moreover, since Housley is completely silent as to the desirability of isolating these compounds, Housley also cannot provide any expectation that these compounds would exhibit any advantageous properties. As such, Housley and Jeffery, in combination, would not have provided a reason to isolate the claimed compounds, much less any expectation that advantageous properties would be obtained by isolating the claimed compounds. Thus, claims 2, 4-6, 74, or 76-78 are not obvious over the combination of Housley and Jeffery.

In his last Office Action, the Examiner alleges that "even though, [Jeffery] does not mention those [stereo]centers, the carbon having four different atoms on it, automatically is entitled to the stereocenters." (Office Action dated March 30, 2008, page 3). However, by following the Examiner's rationale, stereoisomers would always be *prima facie* obvious over a corresponding racemate merely because it is generally known that stereocenters exist when an atom has four different substituents. However, this rationale cannot stand because, as was known to those skilled in the art at the time of the invention, changes in stereochemistry may result in profound differences in a compound's properties. Even if a racemate is found to have a desirable pharmacological profile (*i.e.*, high efficacy and low incidence of side

[7] Indeed, as discussed, *infra*, Jeffery actually teaches away from these compounds.

effects), it is still necessary to identify a reason that would have prompted one skilled in the art to isolate the stereomerically pure compound, as well as a reasonable expectation that the stereoisomer would exhibit the desired pharmacological profile. This is because, for example, the pharmacological activity of a racemate may lie in one enantiomer exclusively, both enantiomers equally, or in both enantiomers in unequal proportions. Moreover, as is known to those skilled in the art, the active stereoisomer of a compound may very well be responsible for that particular compound's side effects. As such, absent evidence to the contrary, one skilled in the art would not have any reason or expectation of success with regard to any of these possibilities.

Further, the Examiner's rationale amounts to the same kind of inflexible *per se* rule that was rejected by the Supreme Court in *KSR* and is inconsistent with the standard of obviousness applied by the Federal Circuit and District Courts in cases following *KSR*. As discussed, *KSR* rejects the use of "rigid and mandatory formulas" and requires a showing that (1) there would have been a reason to pursue the claimed invention; and (2) there would have been a reasonable expectation of success. (*Id.*). Moreover, even prior to *KSR*, **this Board has rejected the proposition that stereoisomers are *per se* obvious over a prior disclosure of the corresponding racemate**, as evidenced by this Board's decision in *Ex Parte Holy*.[8] (2004 WL 77012). In *Holy*, claims directed to a stereomerically pure isomer were rejected as allegedly obvious by the Examiner over a reference that disclosed the corresponding racemate. Similar to the Examiner in the instant case, the Examiner in *Holy* alleged that the stereoisomer "is held as an obvious variant [of the racemate] in view of its very close structural similarity and the fact that one skilled in the art would recognize the existence of such isomers and expect one of a pair to perform better over the other." (*Id.*). Further, similar to the Examiner in the instant case, the Examiner in *Holy* relied on *In re Adamson* and alleged that an optically pure form of a compound is *per se* obvious. (*Id.*). This Board rejected these allegations as a basis for obviousness and reversed the Examiner's rejection. As this Board explained:

> in order to make a prima facie case of obviousness based on the structural similarity, in this case similarity between the claimed optical isomer and its racemate taught by the prior art, not only must the structural similarity exist, but the prior art must also provide reason or motivation to make the claimed compound.

[8] *See* Evidence Appendix, **Exhibit A**.

(*Id.* (emphasis added)). With regard to the Examiner's reliance on *In re Adamson*, this Board cautioned that "[o]ne cannot rely on case law alone...to provide the motivation to modify a prior art compound." (*Id.*).

Thus, in view of the legal precedent set forth in *KSR*, as well as this Board in *Holy*, the Examiner's allegation that stereoisomers are *per se* obvious over a prior disclosure of the corresponding racemate cannot form the basis of an obviousness rejection. Indeed, such an allegation amounts to an improper "rigid and mandatory" rule because no *per se prima facie* case of obviousness may be alleged based on any type of structural similarity alone.

While the Examiner further states that "especially in view of Housley, one of ordinary skill in the art would be motivated to isolate [stereoisomers]," the Examiner has pointed to column 5, lines 48-60 and the compound disclosed on column 7, lines 48-49 of Housley. Appellants respectfully submit that these portions do not support the rejection. (Office Action dated March 20, 2008; *see also* Office Action dated September 12, 2007). For example, the disclosure in column 5, lines 48-60 merely discloses that a compound may exist as stereoisomers whenever there is a chiral atom – a concept that was already generally known in the art. However, this disclosure does not provide any reason to specifically isolate compounds 4, 5a, and 5b of Jeffery, nor does it provide any expectation that these compounds would be advantageous.

In addition, the compound disclosed on column 7, lines 48-49 is not encompassed by claims 2, 4-6, 74, or 76-78. To the extent the Examiner is alleging that this compound is structurally similar, the rejection is improper. As set forth above, an allegation based on structural similarity, in the absence of a showing that one skilled in the art would have had a reason to isolate a claimed compound and a showing that the claimed compound would be expected to be advantageous, is an improper basis for rejection under 35 U.S.C. §103.

With regard to the other compounds encompassed by these claims, *i.e.*, 1-hydroxylated and 7-hydroxylated derivatives of alkylamino and dialkylamino sibutramine, the Examiner merely alleges that these compounds are obvious because "the instant claims are directed to structurally similar compounds" when compared to compound 5a of Jeffery. (Office Action dated March 20, 2008). In this regard, Appellants respectfully point out that allegations of structural similarity alone are an improper basis for rejection under 35 U.S.C. §103. Indeed, the Examiner's line of reasoning – that structurally similar compounds would

be expected to exhibit similar pharmacological properties – was specifically rejected as a basis for an obviousness determination by the Federal Circuit in the wake of *KSR*. (*Takeda Chemical Industries, Ltd. v. Alphapharm Pty.*, Ltd. 492 F.3d 1350, 1356 (C.A.Fed. (N.Y.)), 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007)). Specifically, in *Takeda*, even though the Federal Circuit acknowledged that a known compound's homologs, analogs, or isomers "often have similar properties" and that chemists may "contemplate making them to try to obtain compounds with improved properties," the Court nonetheless emphasized that "in order to find a prima facie case of unpatentability in such instances, a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention [is] also required." (*Id.* (internal citations omitted)(emphasis added)). Indeed, the Court cautioned "'that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other.'" (*Id.* at 1361 (quoting *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985))). Thus, the current law of obviousness in cases concerning structurally similar compounds "requires a showing of 'adequate support in the prior art' for the change in structure." *Id.* at 1356 (quoting *In re Grabiak*, 769 F.2d at 729). As the Court stated:

> in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

(*Id.* at 1357 (emphasis added)).

As such, contrary to the Examiner's allegations, it is clear that any alleged structural similarity of stereoisomers can not form the basis of an obviousness rejection. Indeed, such a basis amounts to a "rigid and mandatory" formula, which was expressly rejected by *KSR*. The proper analysis requires the Examiner to show that there would have been a reason to pursue the claimed compounds and that there would have been a reasonable expectation that the compounds would possess advantageous properties. These principles were applied even prior to *KSR* and *Takeda* by the courts – including this Board – because it was recognized that even slight modifications in structure can have substantial effects on the properties of a compound. (*See, e.g., In re Langer*, 465 F.2d 896, 175 U.S.P.Q. 169 (CCPA 1972) (claims to a polymerization process using an amine were held unobvious over a similar prior art process because of steric differences even though claimed amine differed by only 3 carbon atoms); MPEP § 2144.09 (citing *Ex parte Blattner*, 2 U.S.P.Q.2d 2047 (Bd. Pat. App. & Inter 1987))

(claims directed to compounds containing a 7-membered ring held unobvious over a reference which taught 5- and 6- membered ring homologs of the claimed compounds) MPEP § 2144.09 (citing *In re Mills*, 281 F.2d 218, 126 U.S.P.Q. 513 (C.C.P.A. 1960)) (claims to C1 alkyl sulfate held to be unobvious over prior art disclosure of C8 to C12 alkyl sulfates); MPEP § 2144.09 (citing *Ex parte Mowry*, 91 U.S.P.Q. 219 (Bd. App. 1950))(claimed cyclohexylstyrene held not to be *prima facie* obvious over prior art isohexylstyrene); MPEP § 2144.09 (citing *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992)) (obviousness rejection of novel dicamba salt with acyclic structure reversed even though prior art reference taught broad prior genus encompassing claimed salt because disclosed examples of genus were dissimilar in structure, lacking an ether linkage or being cyclic)). Thus, the Examiner has failed to show how 1-hydroxylated and 7-hydroxylated derivatives of alkylamino and dialkylamino sibutramine would have been obvious.

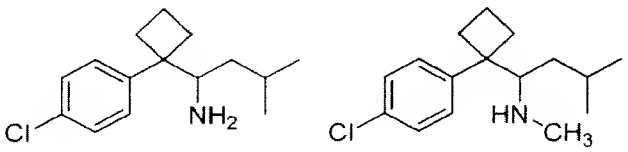
In sum, the Examiner has not established a *prima facie* case of obviousness for claims 2, 4-6, 74, or 76-78. First, Jeffery does not teach any of the compounds encompassed by these claims. Second, the Examiner has not provided a legally sufficient reason that would have prompted one skilled in the art to isolate the claimed compounds, nor has the Examiner provided a teaching that would have provided one skilled in the art the expectation that the claimed compounds would have advantageous properties. Instead, all arguments made by the Examiner during the prosecution of this case are based on mere allegations of structural similarity, as discussed above. However, it is clear from the Supreme Court's decision in *KSR*, the Federal Circuit's decision in *Takeda*, and this Board's decision in *Holy* that **allegations of structural similarity alone do not provide an adequate "reason" or "reasonable expectation of success" for purposes of establishing a *prima facie* case of obviousness**. For these reasons alone, the Examiner's erred in rejecting claims 2, 4-6, 74, and 76-78. Thus, Appellants respectfully request that this Board reverse the Examiner's rejection.

2. Even assuming, *arguendo*, a *prima facie* case were established, Jeffery rebuts such a *prima facie* case because it teaches away from the instantly claimed compounds.

Even assuming, *arguendo*, a *prima facie* case were established, Jeffery rebuts such a *prima facie* case because it teaches away from claims 2, 4-6, 74, and 76-78. As explained by the Federal Circuit following *KSR*, "[w]hen a patent applicant puts forth rebuttal evidence,

the Board must consider that evidence." (*In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007) (emphasis added); *see also* MPEP §2145). Such rebuttal evidence includes "evidence that the prior art teaches away from the claimed invention in any material respect." (*Id.* at 1351, (citing *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003))). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference..." (*In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130 (Fed. Cir. 1994)). Further, "[a] reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." (*Id.* (emphasis added)). As set forth below, Jeffery teaches away from the claims 2, 4-6, 74, and 76-78 because one skilled in the art, upon reading Jeffery, would have been discouraged from pursuing the compounds recited by these claims. Indeed, Jeffery would have suggested that use of these compounds would unlikely be productive.

First, as repeatedly noted by Appellants during the prosecution of this case, Jeffery discloses that "[s]ibutramine undergoes rapid and extensive metabolism in humans, initially resulting in the demethylated amines [shown below in Figure 5]." (Jeffery, page 2583, left column). Importantly, Jeffery discloses that "the pharmacological activity of sibutramine is mediated predominantly by these two metabolites." (*Id.*). Thus, rather than focus on the compounds recited by claims 2, 4-6, 74, and 76-78, one skilled in the art would have focused on these non-hydroxylated metabolites. This disclosure alone would have taught away from the instant compounds.



As disclosed in Jeffery, the pharmacological activity of sibutramine is mediated predominantly be these metabolites, which are not encompassed by claims 2, 4-6, 74, and 76-78. These seemingly "better" alternatives would have taught those skilled in the art away from the instant compounds.

Figure 5. Active metabolites of sibutramine.

Indeed, the Federal Circuit has refused to find claims directed to compounds obvious when the prior art discloses better alternatives to the claimed compounds. For example, in

Yamanouchi Pharmaceutical Co. Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1344-45, 56 U.S.P.Q.2d 1641 (Fed. Cir. 2000), the Federal Circuit held that the selection of a compound as a lead candidate for drug development was not obvious even though this compound exhibited activity that was three times greater than the compound considered to be the benchmark. In explaining its determination, the Court focused on the disclosure of better alternatives that were up to ten times more active than the benchmark compound and held that the required motivation was not shown. (*Id.*).

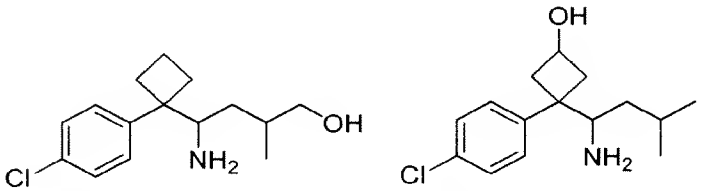
Even after *KSR*, the Federal Circuit has not changed its position that the disclosure of better alternatives support the nonobviousness of a claimed compound. (*Takeda*, 492 F.3d at 1358-60). For example, in *Takeda*, the Federal Circuit affirmed the District Court's determination that it was not obvious to select a compound, in part because the prior art disclosed better alternatives. (*Id.*). Specifically, the Federal Circuit affirmed the District Court's conclusion that the selection of a compound was not obvious, in part because the prior art disclosed "three specific compounds that were deemed most favorable..." (*Id.* at 1358). In reaching this determination, the Federal Circuit stated "[n]otably, [the selected compound] was not identified [by the prior art] as one of the three most favorable compounds." (*Id.*).

Since Jeffery discloses that the two demethylated metabolites of sibutramine are predominantly responsible for the activity of sibutramine, those skilled in the art would have considered these metabolites to be better alternatives to the claimed hydroxylated metabolites. For this reason alone, Jeffery teaches away from claims 2, 4-6, 74, and 76-78, and the Examiner's rejection should be reversed.

Second, Jeffery specifically discloses that the 1-hydroxyl and 7-hydroxyl sibutramine metabolites do not play a major role in contributing to the pharmacological activity of sibutramine. For example, as discussed, *supra*, Jeffery discloses that the demethylated metabolites, which do not have any hydroxyl group, are "predominantly" responsible for the pharmacological activity of sibutramine.[9] Notably, Jeffery discloses that "[f]urther oxidative

[9] On pages 3 and 4 of the Office Action dated February 9, 2005, the Examiner alleged that "Applicants argue that the Jeffery [reference] teach that their compounds are pharmacologically inactive. The Examiner did not find such a statement in the reference." It is noted that Appellants did not assert that the compounds were completely inactive. Instead, Appellants pointed out that "Jeffery discloses that pharmacological activity of sibutramine is mediated predominantly by sibutramine metabolites other than those claims in this application." (Appellants' Response dated January 18, 2005, page 3). In other words, the claimed compounds do not play a

metabolism [of the demethylated sibutramine metabolites] results in the hydroxylated amines 4 and 5a which are **excreted** as glucuronide conjugates." (Jeffery, page 2583, left column (emphasis added), *see also* Figure 6, *infra*). As such, Jeffery teaches away from the instant claims because those skilled in the art would not have even selected 1-hydroxyl or 7-hydroxyl sibutramine – much less a stereomerically pure 1-hydroxyl or 7-hydroxyl sibutramine – as a lead candidate for further investigative study.[10] Indeed, because 1-hydroxyl and 7-hydroxyl sibutramine do not play a major role in the activity of sibutramine, and because these compounds are actually excreted, one skilled in the art clearly would have been "discouraged" from pursuing these compounds as candidates for pharmaceutical uses. It is axiomatic that if one skilled in the art would not have even started with 1-hydroxyl or 7-hydroxyl sibutramine, one skilled in the art would not have had any impetus to make the structural modifications required to arrive at the claimed compounds.



Jeffery compound 4
1-hydroxy-sibutramine

Jeffery compounds 5a
7-hydroxy-sibutramine

Jeffery discloses that these compounds "are excreted as glucuronide conjugates." Thus, Jeffery teaches away from 1-hydroxylated and 7-hydroxylated sibutramine derivatives.

Figure 6. Compounds 4 and 5a of Jeffery

In this regard, this Board has previously held that a reference that teaches that a metabolite does not play a major role in pharmacological activity establishes the non-obviousness of the use of such metabolite for the corresponding pharmacological purpose. Specifically, in *Ex parte Barberich*[11], Appeal No. 2005-0906, this Board considered the patentability of claims directed to methods of treating disorders ameliorated by the inhibition of serotonin reuptake at the H-HT$_2$ and/or the inhibition of dopamine reuptake at D$_2$ receptors

---

major role in the pharmacological activity. Such a disclosure is clearly sufficient to evidence the teaching away from the instant claims, as will be discussed.

[10] The Examiner has relied on these very same compounds in alleging that the instant claims are *prima facie* obvious.

[11] *See* Evidence Appendix, **Exhibit B**.

with sulfoxide and sulfone metabolites of ziprasidone. This Board held that the claims were not obvious in view of a reference that disclosed that the "the affinities of the sulfoxide and sulfone metabolites for 5-HT_2 and D_2 receptors are low..." (*Id.*, internal quotations omitted). Moreover, the Board rejected the Examiner's argument that the reference's disclosure is not necessarily "an indication that [the sulfoxide and sulfone metabolites] are void of any value for the same therapeutic purpose as ziprasidone." (*Id.*). As this Board explained: "[the reference], although arguably teaching that the sulfone and sulfoxide metabolites have some affinity for the 5-HT_2 and D_2 receptors, specifically teaches that the affinities are low as compared to ziprasidone...and thus [the reference] would not motivate the ordinary artisan [to pursue the claimed invention]." (*Id.*).

In the instant case, similar to *Baberich*, a reference (*i.e.*, Jeffery) discloses that the claimed compounds do not play a major role in the desired activity. Thus, similar to *Baberich*, while Jeffery may arguably teach that the claimed compounds have some pharmacological activities, it "specifically teaches that the [activities] are low." (*Id.*). Thus, Jeffery would have negated any expectation that the compounds of claims 2, 4-6, 74, and 76-78 would be efficacious. Consequently, similar to *Barberich*, the instant claims cannot be obvious.

On the basis of the above, even if, *arguendo*, this Board finds that the Examiner established a *prima facie* case of obviousness, sufficient evidence of teaching away to rebut any presumption of obviousness was provided by Appellants. Thus, Appellants respectfully request that this Board reverse the Examiner's rejection.

D. The Examiner erred in rejecting in rejecting the subject matter recited in claims 3, 75, and 79-82 as allegedly obvious over Jeffery and Housley.

The Examiner erred in rejecting the subject matter recited in instant claims 3, 75, and 79-82 as allegedly obvious over Jeffery and Housley because:

1. The Examiner did not establish a *prima facie* case of obviousness; and

2. Even assuming, *arguendo*, a *prima facie* case were established, Jeffery rebuts such a *prima facie* case because it teaches away from the instantly claimed compounds.

1. The Examiner has not established a *prima facie* case of obviousness.

All legal principles discussed above regarding the law of obviousness also apply to the patentability of claims 3, 75, and 79-82. These discussed principles are incorporated herein by reference.

The Examiner alleges that the subject matter recited by the 3-hydroxyl claims are *prima facie* obvious over Jeffery and Housley. (Office Action dated March 20, 2008, page 3). However, as set forth below, the Examiner has not established a *prima facie* case of obviousness because (1) the Examiner has not identified a reason that would have prompted a person skilled in the art to make or use the instant compounds; and (2) the Examiner has not articulated why one skilled in the art would have had a reasonable expectation that the claimed compounds would be advantageous.

First, Jeffery does not disclose any of the compounds encompassed by claim 3. In addition, Jeffery would not have provided any reason that would have provided any hint at the desirability of these compounds, or a pharmaceutical composition comprising these compounds. Further, Jeffery would not have provided those skilled in the art with a reasonable expectation that the claimed 3-hydroxyl sibutramine derivatives could be pharmaceutically advantageous.

The Examiner alleges that in view of compounds 4 and 5a of Jeffery:

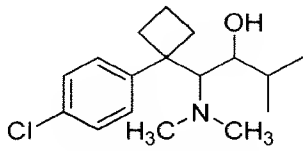
> [i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain compounds with the generic structure of the reference, because the reference structure is structurally so similar to those claimed herein, except the OH position is different, with the reasonable expectation of achieving a successful composition, absent evidence to the contrary. Note that positional isomers are prima facie obvious.

(Office Action dated December 10, 2003 (citing *In re Norris* 179 F.2d 970 (C.C.P.A. 1950))).

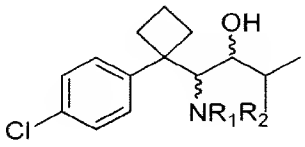
As set forth above, allegations of structural similarity can not form the basis of an obviousness rejection. Contrary to the Examiner's allegation, positional isomers are not *prima facie* obvious. Such an allegation amounts to a "rigid and mandatory" formula, which was expressly rejected by the Supreme Court in *KSR* as a standard for obviousness. Instead, as the Federal Circuit made clear in *KSR*, in the context of chemical compounds, there must

have been a reason to make the structural modifications required to arrive at the claimed compounds. Such a "reason" is completely lacking from Jeffery, as discussed *supra*.

Second, Housley does not cure the defects of Jeffery. While the Examiner points to the compound on column 7, lines 48-49 of Housley ("the dimethyl derivative"), this compound is not encompassed by any of the instant claims. As shown in Figure 7 below, the instant claims recite that when R_1 and R_2 are both methyl, the compound is stereomerically pure.



Compound disclosed in Housley cited by Examiner



claims 3 and 75 when R_1 and R_2 are both methyl, the compound is stereomerically pure

Figure 7.

Further, Housley would not have provided any reason for those skilled in the art to select the dimethyl compound from the large number of compounds disclosed in Housley, nor would Housley have provided any expectation of success. As pointed out to the Examiner, formula I of Houlsey defines a genus that encompasses millions of compounds. (Housley, column 1). Indeed, by defining its genus using terms such as "optionally substituted hydrocarbon group," without any limits as to the number of carbon atoms of the hydrocarbon group, Housley discloses a genus that would encompass an infinite number of species. (*See, e.g.*, Housley, column 1, lines 13-27). Even while Housley discloses the dimethyl derivative as a species, the dimethyl derivative is buried in a list of over 200 other compounds. (*See, e.g.*, Housley, columns 5-12). Yet Housley is completely silent as to the desirability of the dimethyl derivative. As such, one skilled in the art would not have found any reason to specifically focus on the dimethyl derivative.

As well settled, one skilled in the art would not find a "reason" to select a species or subspecies from a genus unless there was "[s]ome motivation to select the claimed species or subgenus [from] the prior art." (MPEP §2144.08; *see also In re Deuel*, 51 F.3d 1552, 1558-9, 34 USPQ2d 1210 (Fed. Cir. 1995) ("No particular one of these DNA's can be obvious unless

there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.") (emphasis added); *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994) ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences corresponds to [a gene], the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.")).

This principle has not changed after the *KSR* decision, as evidenced by the Federal Circuit's decision in *Takeda*. In *Takeda*, the Court held that it was not obvious to select one compound out of a prior art reference that disclosed a large number of compounds, in part because "[r]ather than identify predictable solutions...the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." ((*Id*) (emphasis added)). As discussed above, the Court emphasized that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie obviousness of a new claimed compound." ((*Id.*) (emphasis added)).

Similar to *Takeda*, Housley discloses "a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." Similar to *Takeda*, Housley does not "identify predictable solutions," and, instead, is completely silent as to the desirability of selecting the dimethyl derivative. Thus, similar to *Takeda*, the instant claims are not obvious because one skilled in the art would not have found any reason to select the dimethyl derivative.

Moreover, Housley would not have provided the requisite expectation of success. As discussed above, the Federal Circuit, following *KSR*, articulated guidelines for determining "whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious." (*PharmaStem*, 491 F.3d at 1364). As the Federal Circuit explained:

> [A]n invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.*, (citing *In re O'Farrell*, 953 F.2d 894, 903 (Fed.Cir. 1988)) (internal quotations omitted)).

While Housley discloses the dimethyl derivative, there is no teaching or suggestion whatsoever that would have provided the expectation that singling out the dimethyl derivative from the millions of compounds disclosed in genus of Formula I or, at the very least, from the list of over 200 individually listed compounds, would provide a compound that would be pharmaceutically advantageous. Since such a teaching or suggestion is absent in Housley, or in prior art in general for that matter, the only way one skilled in the art could arrive at the compounds recited by claim 3 is to "try each of numerous possible choices" disclosed in Housley, without any "direction as to which of many possible choices is likely to be successful." (*Id.*). This is precisely what the Federal Circuit warned does not provide a reasonable expectation of success in *PharmaStem*.

Further, even assuming, *arguendo*, that one skilled in the art would have had the requisite reason and reasonable expectation of success to single out the dimethyl derivative, nothing would have provided a reason or reasonable expectation of success with regard to selecting the stereomerically pure form of the dimethyl derivative or with regard to making the molecular modifications necessary to arrive at the other compounds encompassed by the instant claims. Again, to the extent the Examiner relies on allegations of structural similarity as a purported reason or expectation of success, the rejection is improper because such allegations have been rejected as a basis for a determination of obviousness, as discussed above.

The Examiner alleges that "Applicants' allegation that millions of compounds can be generated from Housley's reference appear to be exaggerated, especially when the examiner has particularly pointed out to the specific compound in column 7. There is certainly no lack of motivation herein, especially when the chiral centers exist and there are well known methods of deriving the isomers." (Office Action dated March 20, 2008). These allegations do not form a proper legal basis for supporting a rejection under 35 U.S.C. §103.

First, as discussed above, Housley does disclose a genus that encompasses millions of compounds because the genus allows for substitution without limit. Second, the Examiner's allegation that the instant claims are obvious because "the examiner has particularly pointed out to the specific compound" is clearly a rejection based on hindsight analysis, which is

improper. Given that Housley and Jeffery does not provide any teaching that would have directed those skilled in the art to single out the dimethyl derivative, Appellants fail to see how at the time of the invention, *i.e.*, prior to the disclosure of the compounds of the instant application, the Examiner or those skilled in the art could have possibly had the insight to single out the dimethyl derivative.[12] Third, as discussed above, the mere fact that chiral centers exist in a compound does not provide a legally sufficient reason or expectation of success with regard to selecting a stereoisomer. In this regard, Appellants point out that this allegation amounts to the proposition that no stereoisomers are ever *prima facie* non-obvious. This is flatly contrary to the post-*KSR* Federal Circuit decisions wherein it was held that expectation of success is still required for *prima facie* case of obviousness, as discussed above.

In sum, the Examiner has failed to establish a *prima facie* case of obviousness for claims 3, 75, and 79-82 because: (1) Jeffery does not teach any of the compounds encompassed by these claims, nor does it provide any reason to make the claimed compounds or reasonable expectation that these compounds would be pharmacologically advantageous; and (2) Housley does not cure the defects of Jeffery because, even while Housley discloses the dimethyl derivative, Housley defines a genus that discloses an infinite number of compounds, or at the very least, discloses a list of over 200 specific compounds, but does not provide any reason or expectation of success regarding singling out the dimethyl derivative. For these reasons alone, the Examiner's erred in rejecting claims 3, 75, and 79-82. Thus, Appellants respectfully request that this Board reverse the Examiner's rejection.

2. Even assuming, *arguendo*, a *prima facie* case were established, Jeffery rebuts such a *prima facie* case because it teaches away from the instantly claimed compounds.

Even assuming, *arguendo*, a *prima facie* case were established, Jeffery rebuts such a *prima facie* case because it teaches away from the instantly claimed compounds.

As discussed above, Jeffery discloses that "[s]ibutramine undergoes rapid and extensive metabolism in humans, initially resulting in the demethylated amines [shown above in Figure 5]." (Jeffery, page 2583, left column). Importantly, Jeffery discloses that "the

[12] Appellants also wish to take this opportunity to note that during a phone call with the Examiner, the undersigned was requested by the Examiner to identify the dimethyl derivative. In other words, it appears that even while the Examiner had the Housley reference and the pending claims in front of him, the Examiner was unable to single out the dimethyl derivative without the specific direction from Appellants.

pharmacological activity of sibutramine is mediated predominantly by these two metabolites." (*Id.*). Thus, one skilled in the art would have had a reason to focus on these metabolites, rather than focus on the instantly claimed derivatives. As such, this disclosure alone would have taught away from the instant compounds.

As discussed above, the Federal Circuit has refused to find claims directed to compounds obvious where the prior art discloses better alternatives to the claimed compounds, as evidenced by *Yamanouchi* and *Takeda*. Since "better" alternatives are indeed disclosed in Jeffery, the claims 3, 75, and 79-82 are not obvious. As such, Appellants respectfully request that this Board reverse the Examiner's rejection.

E. Conclusion

For at least the reasons above, Appellants respectfully submit that the Examiner erred in rejecting the subject matter of the instant claims. Appellants, therefore, request that the Examiner's rejection under 35 U.S.C. 103 be reversed and that the instant claims be allowed.

A fee of $510.00 is believed due for the submission of this paper. However, if any additional fees are due, the Director is authorized to charge such fees to Deposit Account No. 50-3013.

Respectfully submitted,

Date: **August 18, 2008**

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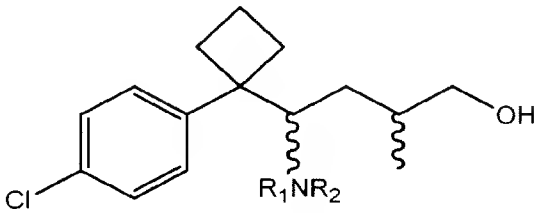
VIII. CLAIMS APPENDIX

A. Clean Copy of Claims

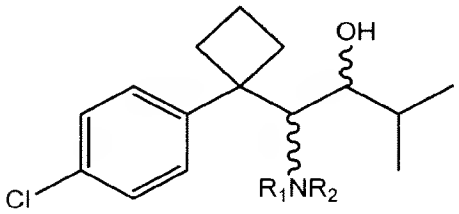
1. (Canceled)

2. (Currently Amended) A compound of the formula:



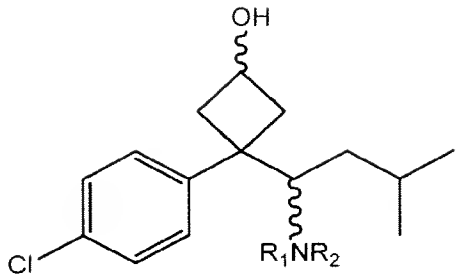
or a pharmaceutically acceptable salt, solvate, or hydrate thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if R_1 and R_2 are both hydrogen, the compound is stereomerically pure.

3. (Currently Amended) A compound of the formula:



or a pharmaceutically acceptable salt, solvate, or hydrate thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if R_1 and R_2 are both methyl, the compound is stereomerically pure.

4. (Currently amended) A compound of the formula:



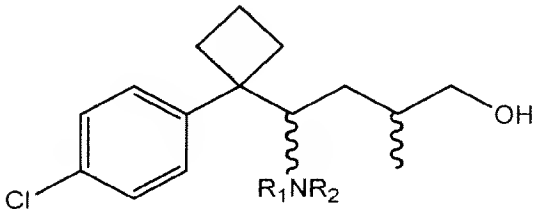
or a pharmaceutically acceptable salt, solvate, or hydrate thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if both R_1 and R_2 are hydrogen, the compound is stereomerically pure.

5. (Previously presented) The compound of claim 2 or 4, wherein at least one of R_1 or R_2 is hydrogen.

6. (Previously presented) The compound of claim 2 or 4, wherein at least one of R_1 or R_2 is methyl.

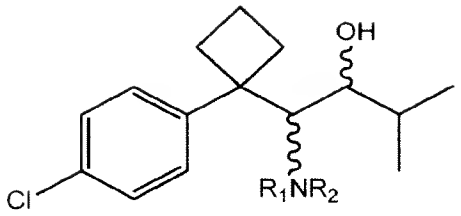
7-73. (Canceled).

74. (Currently amended) A pharmaceutical composition comprising a compound of the formula:



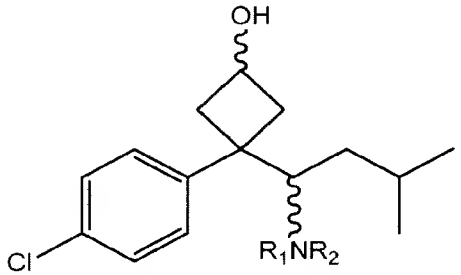
or a pharmaceutically acceptable salt, solvate, or hydrate thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if R_1 and R_2 are both hydrogen, the compound is stereomerically pure.

75 (Currently amended A pharmaceutical composition comprising a compound of the formula:



or a pharmaceutically acceptable salt, solvate, or hydrate, thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if R_1 and R_2 are both methyl, the compound is stereomerically pure.

76. (Currently amended) A pharmaceutical composition comprising a compound of the formula:



or a pharmaceutically acceptable salt, solvate, hydrate thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if both R_1 and R_2 are hydrogen, the compound is stereomerically pure.

77. (Previously presented) The pharmaceutical composition of claim 74 or 76, wherein at least one of R_1 or R_2 is hydrogen.

78. (Previously presented) The pharmaceutical composition of claim 74 or 76, wherein at least one of R_1 or R_2 is methyl.

79. (New) The compound of claim 3, wherein at least one of R_1 or R_2 is hydrogen.

80. (New). The compound of claim 4, wherein at least one of R_1 or R_2 is methyl.

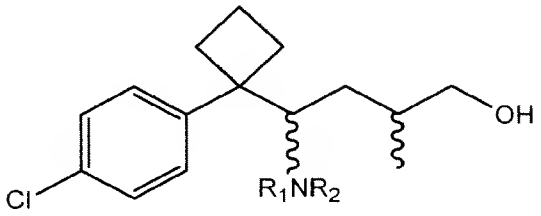
81. (New) The pharmaceutical composition of claim 75, wherein at least one of R_1 or R_2 is hydrogen.

82. (New) The pharmaceutical composition of claim 75, wherein at least one of R_1 or R_2 is methyl.

B. Marked-Up Copy of Claims

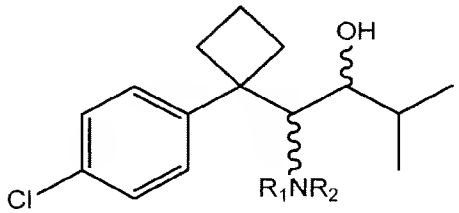
1. (Canceled)

2. (Currently amended) A compound of the formula:



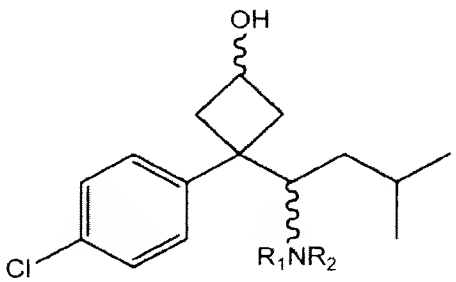
or a pharmaceutically acceptable salt, solvate, or hydrate~~, clathrate, or prodrug~~ thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if R_1 and R_2 are both hydrogen, the compound is stereomerically pure.

3. (Currently Amended) A compound of the formula:



or a pharmaceutically acceptable salt, solvate, or hydrate~~, clathrate, or prodrug~~ thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if R_1 and R_2 are both methyl, the compound is stereomerically pure.

4. (Currently Amended) A compound of the formula:



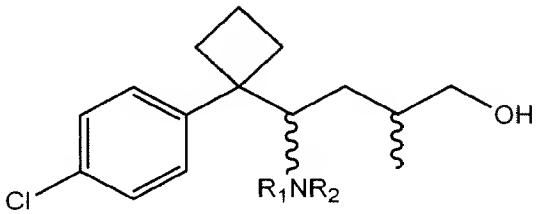
or a pharmaceutically acceptable salt, solvate, or hydrate~~, clathrate, or prodrug~~ thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if both R_1 and R_2 are hydrogen, the compound is stereomerically pure.

5. (Previously presented) The compound of claim 2~~, 3,~~ or 4, wherein at least one of R_1 or R_2 is hydrogen.

6. (Previously presented) The compound of claim 2~~, 3,~~ or 4, wherein at least one of R_1 or R_2 is methyl.

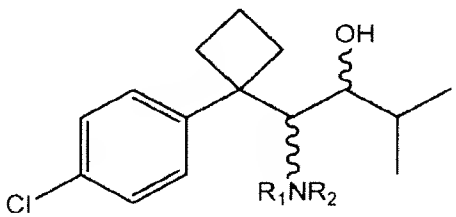
7-73. (Canceled).

74. (Currently amended) A pharmaceutical composition comprising a compound of the formula:



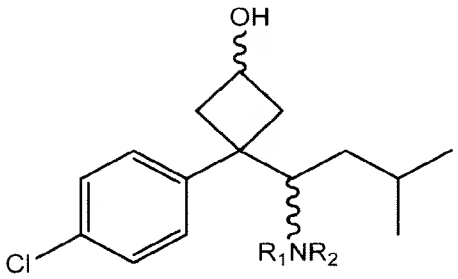
or a pharmaceutically acceptable salt, solvate, or hydrate~~, clathrate, or prodrug~~ thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if R_1 and R_2 are both hydrogen, the compound is stereomerically pure.

75 (Previously Presented) A pharmaceutical composition comprising a compound of the formula:



or a pharmaceutically acceptable salt, solvate, or hydrate~~, clathrate, or prodrug~~ thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if R_1 and R_2 are both methyl, the compound is stereomerically pure.

76. (Previously presented) A pharmaceutical composition comprising a compound of the formula:



or a pharmaceutically acceptable salt, solvate, or hydrate~~, clathrate, or prodrug~~ thereof, wherein each of R_1 and R_2 is independently alkyl or hydrogen, provided that if both R_1 and R_2 are hydrogen, the compound is stereomerically pure.

77. (Previously presented) The pharmaceutical composition of claim 74~~, 75,~~ or 76, wherein at least one of R_1 or R_2 is hydrogen.

78. (Previously presented) The pharmaceutical composition of claim 74~~, 75,~~ or 76, wherein at least one of R_1 or R_2 is methyl.

79. (New) The compound of claim 3, wherein at least one of R_1 or R_2 is hydrogen.

80. (New). The compound of claim 4, wherein at least one of R_1 or R_2 is methyl.

81. (New) The pharmaceutical composition of claim 75, wherein at least one of R_1 or R_2 is hydrogen.

82. (New) The pharmaceutical composition of claim 75, wherein at least one of R_1 or R_2 is methyl.

IX. EVIDENCE APPENDIX

Exhibit A: *Ex Parte Holy*, 2004 WL 77012

Exhibit B: *Ex parte Barberich*, Appeal No. 2005-0906.

Exhibit A

Exhibit A

2004 WL 77012 (Bd.Pat.App. & Interf.)

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

Board of Patent Appeals and Interferences
Patent and Trademark Office (P.T.O.)

EX PARTE ANTONIN HOLY, HANA DVORAKOVA, ERIK D. A. DE CLERCQ, JAN M. R. BALZARINI

Appeal No. 2000-1024
Application No. 08/379,551

NO DATE REFERENCE AVAILABLE FOR THIS DOCUMENT

MAX D HENSLEY
GILEAD SCIENCES INC
353 LAKESIDE DRIVE
FOSTER CITY, CA 94404

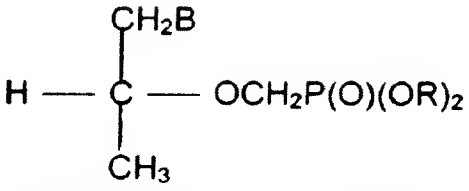
Before WINTERS, GRIMES, and GREEN
Administrative Patent Judges
GREEN
Administrative Patent Judge

ON BRIEF

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 4, 6, 8, 12-19, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94. Claim 1 is representative of the subject matter on appeal, and reads as follows:

1. A compound of the formula:



(IA)

and pharmaceutical salts of such compounds, wherein said compound of formula IA is substan-

tially free of its enantiomer and wherein B is (a) an unsubstituted purine moiety, (b) a substituted purine moiety substituted independently at the 2 and/or 6 and/or 8 position by amino, halogen, hydroxy, alkoxy, alkylamino, dialkylamino, aralkylamino, pyrrolidino, morpholino, piperidino, benzoylamino, azido, mercapto or alkylthio, or (c) the 8-aza analog thereof, and wherein

B is other than a guanine or 2-amino-6-halopurine;

R is H; and aryl in aralkylamino is a 6-10C aromatic group.

Claims 4, 6, 8, 70, 72, 73, 75, 85, 91, 93 and 94 further limit the compound of claim 1. Claims 12-19 are drawn to a method of preparing the compound of claim 1. Claims 45 through 48, 55, 63 and 65 are drawn to specific compounds that fall within the compound of claim 1.

The examiner relies upon the following references:

Hol [*sic*] et al. (Holy (US))	4,808,716	Feb. 28, 1989
Alexander et al. (Alexander)	5,130,427	Jul. 14, 1992
Yu et al. (Yu (US))	5,302,585	Apr. 12, 1994
Vemishetti et al. (Vemishetti)	5,476,938	Dec. 19, 1995
Webb, II et al. (Webb (US))	5,650,510	Jul. 22, 1997
European Patent Applications		
Holy et al. (Holy (EP))	0 253 412	Jul. 18, 1986
Webb, II (Webb (EP))	0 269 847	Jun. 08, 1988
Yu et al. (Yu (EP))	0 452 935	Oct. 23, 1991
Starrett et al. (Starrett)	0 481 214	Apr. 22, 1992

***2** Karrer, Organic Chemistry, 2nd English Edition, pp. 92-102 (1946)

The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, 11th Edition, Article No. 7868, p. 1247 (1989)

In addition, appellants rely upon the following references:

DeClercq et al. (DeClercq), "Antiviral activity of phosphonylmethoxyalkyl derivatives of purine and pyrimidines," Antiviral Research, Vol. 8, pp. 261-272 (1987)

Holy et al. (Holy (1989)), "Phosphonylmethyl Ethers of Nucleosides and Their Acyclic Analogues," ACS Symposium Series, Vol. 401, pp. 51-71 (1989)

Claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Holy (US), Webb (EP or US), Yu (US or EP), Starrett, Holy (EP) and Karrer. Claims 12-19 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Holy (US), Holy (EP), Webb (EP or US), Vemishetti, Alexander, Yu (US or EP) and the Merck Index. Claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 stand rejected under the judicially created doctrine of obviousness-type double patenting over the claims of Holy (US), U.S. Patent No. 4,808,716 (the '716 patent) as combined with Yu (EP or US), Holy (EP), Starrett

and Karrer. Claims 1, 4, 6, 8, 45-48, 55, 63, 65, 72, 73, 75, 85, 91, 93 and 94 stand rejected under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patent No. 5,650,510 (the '510 patent) as combined with Yu (EP or US), Holy (EP), Starrett and Karrer. Finally, claims 1, 4, 6, 70, 72, 85, 91, 93 and 94 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the claims of copending Application No. 07/925,610. After careful review of the record and consideration of the issues before us, we reverse all of the rejections of record except the provisional obviousness-type double-patenting rejection of claims 1, 4, 6, 70, 72, 85, 91, 93 and 94 over copending Application No. 07/925,610.

DISCUSSION

Claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Holy (US), Webb (EP or US), Yu (EP or US), Starrett, Holy (EP) and Karrer. In addition, the obviousness-type double patenting rejections over the '716 patent and the '510 patent as combined with Yu (EP or US), Holy (EP), Starrett and Karrer are included in the analysis of the rejection over the combination of Holy (US), Webb (EP or US), Yu (EP or US), Starrett, Holy (EP) and Karrer as the rejections state that the claims of the patents are "obvious variant[s] of that claimed herein as discussed in the above 103 rejection." Examiner's Answer, page 7. In addition, appellants rely on the patentability of the end product to overcome the rejection of claims 12-19 over the combination of Holy (US), Holy (EP), Webb (EP or US), Vemishetti (US), Alexander (US), Yu (US or EP) and the Merck Index. Thus, that rejection is also encompassed by the following analysis.

*3 Holy (US) is cited by the rejection for teaching a racemic mixture of 2-phosphonomethoxypropyladenine (PMPA). PMPA is included in the range of structures of claim 1. The rejection also references compound 2 in Table 1, as well as a discussion of the applications of the disclosed compounds, such as anti-viral activity, in column 4, lines 14-19 of the Holy (US) patent. The rejection reasons that:

> While the corresponding optical isomer is not particularly disclosed, the claimed R-isomer is held as an obvious variant in view of its very close structural similarity and the fact that one skilled in the art would recognize the existence of such isomers and expect one of a pair to perform better over the other. There is case law regarding the standards of patentability of optical isomers over the corresponding racemic mixture which is on point. See for example, In re Adamson, 125 USPQ 233; Eli Lilly vs. Generix, 174 USPQ 65 regarding the standards of patentability of optical isomers over the corresponding racemic mixture. Note Karrer, cited in Adamson, and applied herein is evidence that it is very well known considerably prior to applicants' effective filing to consider the separation of biologically active racemates in order to determine if one is largely responsible for the desired activity.

Examiner's Answer, page 5.

Webb (EP or US) is apparently cited for teaching derivatives of the compounds as taught by Holy (US). According to the rejection, "Webb does not embrace adenine compound of US Holy but does embrace substituted derivatives thereof having the same sidechain." Examiner's Answer, page 5. Yu (EP or US) is cited for its disclosure of resolution of one of the racemates disclosed by Webb "for elucidation of its antiviral properties," and teaches that the R isomer is "especially effective for treating HIV." Id. at 6.

Holy (EP) was cited for teaching compounds similar to the claimed compounds substituted with different groups, which also have anti-viral activity. Starrett was similarly cited for teaching "that for analogous phosphonate derivatives as claimed herein, substitution with alkyl- on the purine ring system at various ring positions is not a new modification." Id. at 6.

The examiner concludes:

> Thus it would have been obvious to one skilled in the art at the time the instant invention was made to expect instant optical isomers in main claim 1 and claims dependent thereon as well as various 2- and/or 6-substituted purines in independent claims 45-48, 55, 63 to be useful against one or more viruses in view of the close structural similarity and equivalency teachings outlined above.

Id.

*4 The panel would like to initially note that review of the issues on appeal was severely hampered by the lack of claim by claim analysis, i.e., the use of a shot-gun rejection. In rejecting claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 over the combination of Holy (US), Webb (EP or US), Yu, Starrett and Karrer, the examiner apparently cites Holy (EP) and Starrett for their teaching of certain derivatives that are only required in the dependent claims. Moreover, the rejection implies that at a minimum, claim 1 is would have been obvious over Holy alone.

> Most tellingly, in the response to appellants' argument that Webb cannot be combined with Holy, the examiner responds that Webb is not a secondary reference but rather a primary reference applied for showing additional aspects of appellants' invention as obvious, mainly for its teaching of 2,6 diamino phosphonomethoxypropyl purine, but Webb also teaches and claims bases such as 2-amino purine, 8-substituted guanines (guanine per se is excluded in the instant claims) which are within at least claim 1.

Examiner's Answer, page 9.

If Webb was not to be combined with Holy (US), it should have been separately applied, or at least the examiner should have explicitly stated that Webb was being applied in the alternative. The way in which the rejection was laid out, however, makes it difficult to understand, much less rebut and review.

The burden is on the examiner to set forth a prima facie case of obviousness. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). In order to make a prima facie case of obviousness based on the structural similarity, in this case similarity between the claimed optical isomer and its racemate taught by the prior art, not only must the structural similarity exist, but the prior art must also provide reason or motivation to make the claimed compound. See In re Dillon, 919 F. 2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc), In re Mayne, 104 F. 3d 1339, 1341, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997); In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 256 (CCPA 1979). Moreover, the prior art has to enable the ordinary artisan to make the claimed compound. See Payne, 606 F.2d at 314. The rejection over Holy (US), Webb (EP or US), Yu (EP or US), Starrett, Holy (EP) and Karrer does not meet this criteria and thus fails to set forth a prima facie of obviousness.

In the rejection above, the examiner states with respect to the separation of the racemates of Holy (US) that "it is very well known considerably prior to applicants' effective filing to consider the separation of biologically active racemates in order to determine if one is largely responsible for the desired activity," see Examiner's Answer, page 5, but does not set forth any facts or findings to support the motivational statement, especially since all that is currently being claimed is a single isomer, i.e., the R isomer. See In re Lee, 277 F.3d 1338, 1343-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (in reviewing an obviousness rejection, the court noted that "conclusory statements" as to teaching, suggestion or motivation to arrive at the claimed invention "do not adequately address the issue").

*5 With respect to the additional references cited by the examiner for teaching the various other substituents required by the claims, the only motivation that the examiner provides for making the combination is structural similarity. As noted above, however, structural similarity is not enough, but there must also be some teaching, suggestion, or motivation provided in the prior art to make the combination.

Moreover, appellants also argue that the art teaches away from isolating PMPA or PMPDAP from its isomer. Appellants cite Holy (1989) and DeClercq for teaching that PMPA is an inactive product. See Appeal Brief, pages 19-23. The examiner did not find the teaching away references to be persuasive because Holy filed and obtained a patent for PMPA and other compounds on the basis that the compounds are antiviral.

Obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. See In re Kuderna, 426 F.2d 385, 389, 165 USPQ 575, 578 (CCPA 1970); see also In re Shuman, 361 F.2d 1008, 1012, 150 USPQ 54, 57 (CCPA 1966). In assessing the teachings of the prior art references, the examiner should also consider those disclosures that may teach away from the invention. See In re Geisler, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997).

DeClercq states that PMPA is an "inactive product[]". DeClercq, page 264. The examiner dismisses that teaching by arguing that, in context, it appears that DeClercq is referring to the S-isomer. See Examiner's Answer, page 7. When a particular isomer is being referred to by the reference, however, DeClercq seems to indicate as such. Holy (1989) indicates that the replacement of the primary hydroxy group in HPMPA by a methyl group resulted in the loss of activity. See Holy (1989), pages 56-57. Thus, both DeClercq and Holy (1989) teach away from resolving a racemic mixture of PMPA into the currently claimed enantiomer.

In finding that the above prior art references do not teach away from separating a racemic mixture of PMPA into its optically pure isomers, the examiner relies on the Holy (US) patent, apparently bothered by the fact that Holy, who is also an inventor on the instant application, obtained a patent whose claims encompass PMPA. The examiner additionally asserts in support of the rejection that the patent was obtained because the compounds were shown to have antiviral activ- ity.

While PMPA may be encompassed by the group of structures claimed in the Holy (US) patent, that is not dispositive of the issue of whether PMPA has antiviral activity. A claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. § 112, first paragraph. See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976).

***6** In Table 1 of the Holy (US) patent, specifically referred to by the examiner in rejecting the claims at issue, see Examiner's Answer, page 4, certain chemical characteristics are given for compound 2, i.e., PMPA, but the table does not set forth any biological data. The disclosure of Holy relied upon by the examiner as stating that PMPA has biological activity, i.e., column 4, lines 14-19 of the Holy (US) patent, also does not support the examiner's position. That portion of the patent states:

> Some compounds of the general formula I which are the subject of this invention, are important active components of antiviral drugs. An example of such compound is 9-phosphonylmethoxyethyladenine which exhibits a specific activity against DNA-viruses and Maloney sarcoma (PV 3018-85).

(Emphasis added). Thus, the patent does not assert that all of the compounds have antiviral activity, but that some of the compounds may have antiviral activity. When the disclosure of Holy (US) is read in conjunction with the teachings of DeClercq and Holy (1989), which specifically address PMPA, teaching that compounds such as PMPA do not have antiviral activity, the prior art, when read as a whole, teaches away from separating a racemic mixture of PMPA into its optically pure isomers.

In addition, the examiner also relies upon Adamson and Eli Lilly as apparently standing for the proposition that an optically pure form of a compound is per se obvious over a disclosure of a racemic mixture of the compound. See Examiner's

Answer, page 8 ("The motivation to resolve the racemate of Holy is fully supported by the case law previously cited dealing with racemates vs. individual optical isomers."). One cannot rely on case law alone, however, to provide the motivation to modify a prior art compound. "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." In re Rouffet, 149 F.3d 1350, 1356, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998) (citations omitted). In this case, the prior art as a whole, as discussed above, teaches away from making the modification as suggested by the examiner.

Claims 1, 4, 6, 70, 72, 85, 91, 93 and 94 stand provisionally rejected over the claims of co-pending Application No. 07/925,610. As appellants do not present any arguments as to why the rejection is improper, but instead note their intent to file a terminal disclaimer once the copending case is sent to issue, this rejection is affirmed.

CONCLUSION

The rejection of claims 1, 4, 6, 8, 45-48, 55, 63, 65, 70, 72, 73, 75, 85, 91, 93 and 94 over the combination of Holy (US), Webb (EP or US), Yu (EP or US), Starrett, Holy (EP) and Karrer is reversed. For the same reasons, the obviousness-type double patenting rejections over the '716 patent and the '510 patent as combined with Yu (EP or US), Holy (EP), Starrett and Karrer, and the rejection of claims 12-19 over the combination of Holy (EP), Webb (EP or US), Vemishetti, Alexander, Yu (US or EP) and the Merck Index, are also reversed. Finally, the provisional rejection of claims 1, 4, 6, 70, 72, 85, 91, 93 and 94 over the claims of co-pending application No. 07/925,610 is affirmed.

*7 No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART; REVERSED-IN-PART

BOARD OF PATENT APPEALS AND INTERFERENCES

SHERMAN D. WINTERS

Administrative Patent Judge

ERIC GRIMES

Administrative Patent Judge

LORA M. GREEN

Administrative Patent Judge

FN1. According to the Examiner's Answer, claims 49-54, 56-62, 64 and 79 are free of the prior art, with Claim 79 being objected to, and thus these claims are not subject to the instant appeal. See Examiner's Answer, page 2.

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END OF DOCUMENT

Exhibit B

Exhibit B

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte TIMOTHY J. BARBERICH,
PAUL D. RUBIN and WILLIAM E. YELLE

Appeal No. 2005-0906
Application No. 09/527,844

HEARD: July 12, 2005

Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-15 and 50-53. Claims 1 and 5 are representative of the subject matter on appeal, and read as follows:

1. A method of treating or prophylaxis of a disorder ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors in a patient which comprises administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

5. The method of claim 1 wherein the ziprasidone metabolite is ziprasidone sulfoxide or ziprasidone sulfone.

Exhibit B

The examiner relies upon the following references:

Lowe, III et al. (Lowe)	4,831,031	May 16, 1989
Allen et al. (Allen)	5,312,925	May 17, 1994

Davis et al. (Davis), "Ziprasidone," CAPlus Abstract, Copyright 2002, American Chemical Society, referencing CNS Drugs, Vol. 8, No. 2, pp. 153-159 (1997).

Prakash et al. (Prakash), "Metabolism and Excretion of a new Antipsychotic Drug, Ziprasidone, in Humans," Drug Metabolism and Disposition, Vol. 25, No. 7, pp. 863-869 (1997).

Claims 1-4 and 6-9 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Davis. In addition, claims 1-15 and 50-53 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Davis, Lowe, Allen and Prakash. After careful review of the record and consideration of the issues before us, we reverse both rejections of record.

BACKGROUND

Ziprasidone is a highly potent 5-HT_2 and dopamine D_2 receptor antagonist, and while characterized as an antipsychotic, it may also have anxiolytic and antidepressant effects due to ability to inhibit serotonin and noradrenaline uptake. See Specification, page 1. According to the specification, at least twelve metabolites of ziprasidone have been identified in humans, but ~~that~~ the prior art has reported that the metabolites are not active at the D_2 and 5-HT_{2A} receptor sites. See id. at 1-2.

The specification teaches further that "Ziprasidone offers a number of benefits, but unfortunately many adverse effects are associated with its administration. Examples of adverse affects of ziprasidone include, but are not

limited to, nausea, somnolence, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances, male sexual dysfunction, and elevated serum liver enzyme levels. . . . It is thus desirable to find a compound which possesses advantages of ziprasidone but fewer of its disadvantages." Id. at 2-3.

Thus,

> [t]his invention relates to novel methods using, and compositions comprising, ziprasidone metabolites, preferably, ziprasidone sulfoxide and ziprasidone sulfone. These metabolites, prior to the present invention, have been reported to have little or no in vivo activity. The present invention encompasses the in vivo use of these metabolites, and their incorporation into pharmaceutical compositions and single unit dosage forms useful in the treatment and prevention of disorders that are ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors. Such disorders include psychotic and neuroleptic disorders. In a preferred embodiment, ziprasidone metabolites are used in the treatment or prevention of neuroleptic and related disorders in mammals, including humans.

Id. at 3.

The specification describes pharmaceutical compositions comprising ziprasidone metabolites, see id. at 7, as well as methods of preparing the sulfoxide and sulfone metabolites, see id. at 7-8.

DISCUSSION

The issues in this case turn primarily on claim construction—specifically the construction of the term "administering" in the claims.

According to the examiner, the term "administering" should be construed as encompassing the administration of the parent drug, ziprasidone, "because metabolites of ziprasidone are necessarily and inevitably formed under normal

Exhibit B

condition[s] [sic] once ziprasidone is administered to a patient." Examiner's Answer, page 7.

Appellants argue that the examiner's construction of the term "administering" is contrary to its ordinary meaning. See Appeal Brief, page 10. Appellants argue that "administering" refers to "a compound that exists outside of the patient [which] is given, or applied to the patient." Id. Appellants argue further that the examiner's construction is contrary to unambiguous statements made during prosecution "that the term 'administration' or 'administering,' as used in the claims, means giving to a patient a compound as it exists outside of the body." Id. at 13.

During ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification as it would be interpreted by the ordinary artisan. See Phillips v. AWH Corp., 2005 WL 1620331, *9 (Fed. Cir.) (en banc) (citing In re Am. Acad. Of Sci. Tech. Ctr., 367 F.3d 1359, 1364 (Fed. Cir. 2004). Thus, it is "entirely appropriate . . . when conducting claim construction to rely heavily on the written description for guidance as to the meaning of the claims." Id.

In the case before us, the specification focuses entirely on the preparation of ziprasidone metabolites, teaching their synthesis and their incorporation into pharmaceutical compositions. Thus, we construe "administering" as used in the claims as requiring the ex vivo preparation of the ziprasidone metabolite, which

Exhibit B

is then given to the patient, and excluding giving the patient the parent drug ziprasidone.

Claims 1-4 and 6-9 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Davis.[1]

According to the rejection:

> Davis [ ] discloses ziprasidone as an antipsychotic drug having high affinity for serotonin 5-Ht2 and dopamine D2 receptors. Davis [ ] also discloses administration of this drug to patients. Davis further indicates that clinical trials have shown ziprasidone to be effective in treating depression associated with schizophrenia and in reducing anxiety in patients about to undergo dental surgery.

Examiner's Answer, page 3.

It is axiomatic that in order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. See In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). As we have construed "administering" as requiring ex vivo preparation of the ziprasidone metabolite, which is then given to the patient, the Davis abstract does not anticipate the claim, as it does not

[1] We note that the examiner relies solely on the abstract of the Davis article, and from our review of the record, it does not appear that the entire reference has been made of record. "Citation of and reliance upon an abstract is generally inappropriate where both the abstract and the underlying document are prior art." MPEP §706.02 (II) (8th edition, Revision 2, May 2004) Moreover, in order for meaningful appellate review to occur the examiner must present a full and reasoned explanation of the rejection see, e.g., In re Lee, 277 F 3d 1338, 1342, 61 USPQ2d 1430, 1432 (Fed Cir 2002), and that would include analysis of the full underlying document

teach or suggest the use of metabolites of ziprasidone in that manner. The rejection of claims 1-4 and 6-9 under 35 U.S.C. § 102(b) as being anticipated by Davis is thus reversed.

The examiner asserts that the administration of metabolites of ziprasidone is inherent in the administration of the parent drug, ziprasidone. See Examiner's Answer, page 6. The examiner cites Zenith Laboratories, Inc. v. Bristol Myers Squibb, Co., 19 F.3d 1418, 30 USPQ2d 1285 (Fed. Cir. 1994) in support of that assertion, arguing that case "provides that ziprasidone metabolites are necessarily and inevitably formed from the ziprasidone under normal condition[s] [sic]." Id.

We do not disagree that ziprasidone metabolites are "necessarily and inevitably formed" upon the administration of ziprasidone. Claim 1, however, as construed by the panel, requires the ex vivo preparation of the ziprasidone metabolite, which is then given to the patient. That limitation is neither taught nor suggested by the Davis abstract, and thus the Davis reference does not teach the method of claim 1. The court's decision in Zenith Laboratories is not on point, as the claim at issue in that case was drawn to a compound, and the court construed the claimed compound as not being limited to the compound in its preingested form. See id. 19 F.3d at 1422, 30 USPQ2d at 1288. Thus, the decision in that case, as in the case before us, turned on the construction of the claim, and we have construed the claim to exclude giving the patient the parent drug, ziprasidone.

The examiner argues further that instant claim 1 is analogous to a product-by-process claim, as "the product employed in a method claim[ ] may not be limited to the manipulations of the steps creating the product, only the structure implied by the steps, here, ziprasidone metabolites." Examiner's Answer, page 8. According to the examiner, as the patentability of a product does not depend on its method of production, it is irrelevant to the patentability of the claim whether the ziprasidone metabolite is synthesized ex vivo or produced through the metabolism of the parent drug. See Examiner's Answer, pages 8-9.

We do not find the examiner's reasoning to be persuasive. The claims at issue, such as claim 1, are not product-by-process claims. The claim as construed here requires the ex vivo preparation of the ziprasidone metabolite, which is then given to the patient, and as noted above, the Davis abstract does not teach or suggest giving a ziprasidone metabolite, which has been prepared ex vivo, to a patient.

We note that both the examiner and appellants argue that the holding in Schering Corp. v. Geneva Pharmaceuticals, Inc., 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003) supports their position. In that case, the court held that claims drawn to a loratadine metabolite, DCL, were inherently anticipated by prior art drawn to the administration of loratadine, as "DCL necessarily and inevitably forms from loratadine under normal conditions." Id., 339 F.3d at 1378, 67 USPQ2d at 1668. That holding is distinguishable from the case before us

because the claims are not drawn to the metabolite per se, but to a method of administering the metabolite, which we have construed as requiring ex vivo preparation of the metabolite, which is then given to the patient.

In addition, appellants rely on the following language from Schering. See Appeal Brief, page 11.

> Finally, this court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs. With proper claiming, patent protection is available for metabolites of known drugs. . . .
>
> * * *
>
> A skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in *Kratz* and *Bergstrom*, or as a pharmaceutically composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The '233 patent would not provide an enabling disclosure to anticipate such claims because, for instance, the '233 patent does not disclose isolation of DCL.

Id., 339 F.3d at 1378, 67 USPQ2d at 1670.

We note that as we need not rely on the above passage from Schering in reaching our decision today, based on our construction of "administering," we decline to address the argument of whether the above passage is dictum, as argued by the examiner, or necessary to the holding in Schering, as argued by appellants.

Claims 1-15 and 50-53 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Davis, Lowe, Allen and Prakash.

Davis is relied upon as above. The examiner states that "Davis does not specifically teach metabolites of ziprasidone, the amounts (i.e., dosage), or routes of administration as instantly claimed." Examiner's Answer, page 4.

Lowe is relied upon for teaching that ziprasidone and ~~their~~ its pharmaceutically acceptable salts may be administered orally, in the form of tablets or capsules, or parentally. Allen is relied upon for teaching the use of ziprasidone hydrochloride as a neuroleptic agent. See id.

Prakash is cited for teaching the affinity of the sulfone and sulfoxide metabolites of ziprasidone for 5HT2 and D2 receptors. See id.

The rejection concludes:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to employ ziprasidone or any of its known salts or metabolites, including the sulfone and sulfoxides, in a method for treating neuroleptic disorders.
>
> One of ordinary skill in the art would have been motivated to employ ziprasidone or any of its known salts or metabolites in a method of treating neuroleptic disorders, because ziprasidone and ziprasidone hydrochloride are known in treating anxiety, depression associated with schizophrenia and situational anxiety (i.e. anxiety prior to dental surgery). Further, employment of different salts and metabolites of a known active, as an alternative form of different salts and metabolites of a known active, as an alternative form of drug delivery, is within the skill of the artisan and therefore obvious.

Id. at 4-5.

"[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to

combine the relevant teachings of the references.'" In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citation omitted). An adequate showing of motivation to combine requires "evidence that 'a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.'" Ecolochem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1076 (Fed. Cir. 2000).

As argued by appellants, see Appeal Brief, page 16, Prakash teaches that "[t]he affinities of the sulfoxide and sulfone metabolites for 5-HT_2 and D_2 receptors are low with respect to ziprasidone, and are thus unlikely to contribute to its antipsychotic effects." Prakash, abstract. Thus, the skilled artisan would not have been motivated to substitute the sulfoxide and sulfone metabolites for the ziprasidone parent drug in the methods of Davis, Lowe and Allen. The examiner has therefore not established a prima facie case of obviousness, and the rejection of claims 1-15 and 50-53 under 35 U.S.C. § 103(a) is reversed.

The examiner argues that "Prakash teaches that sulfone or sulfoxide metabolites are major metabolites of ziprasidone . . . and that they possess agonistic affinities towards 5HT2 and D2 receptors. Such agonistic properties would have motivated the skilled artisan to employ sulfone or sulfoxide metabolites in a therapeutic regimen absent information to the contrary." Examiner's Answer, page 11. Moreover, according to the examiner, the fact that "sulfone or sulfoxide metabolites have low affinities towards their receptors is not

Exhibit B

persuasive, because such [a] [sic] statement is not an indication that they are void of any value for the same therapeutic purpose as ziprasidone." Id. at 12.

The examiner's argument begs the issue, that is, whether a person of ordinary skill in the art would have been motivated to combine the references to arrive at the claimed invention. Obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. See In re Kuderna, 426 F.2d 385, 389, 165 USPQ 575, 578 (CCPA 1970); see also In re Shuman, 361 F.2d 1008, 1012, 150 USPQ 54, 57 (CCPA 1966). In assessing the teachings of the prior art references, the examiner should also consider those disclosures that may teach away from the invention. See In re Geisler, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997). As discussed above, Prakash, although arguably teaching that the sulfone and sulfoxide metabolites have some affinity for the 5-HT_2 and D_2 receptors, specifically teaches that the affinities are low as compared to ziprasidone, and are thus unlikely to contribute to its antipsychotic effects, and thus Prakash would not motivate the ordinary artisan to substitute ziprasidone metabolites for ziprasidone in the method taught by the other references.

CONCLUSION

Based on our construction of "administering" as used in the claims at issue, we reverse the rejection of claims 1-4 and 6-9 under 35 U.S.C. § 102(b) as being anticipated by Davis. Moreover, we also reverse the rejection of claims 1-15 and 50-53 under 35 U.S.C. § 103(a) as being obvious over the combination of Davis, Lowe, Allen and Prakash, as the examiner failed to set forth a prima facie case of obviousness.

REVERSED

Demetra J. Mills
Administrative Patent Judge)
)
)
)
Eric Grimes) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
Lora M. Green)
Administrative Patent Judge)

Exhibit B

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X. RELATED PROCEEDINGS APPENDIX

None.